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69 - 150 → 15
de aryl ?

WO 02/24650 A2

(54) Title: PYRIDINONE AND PYRIDINETHIONE DERIVATIVES HAVING HIV INHIBITING PROPERTIES

(57) Abstract: The present invention is concerned among others with compounds of formula (I), the N-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and stereochemically isomeric forms thereof, wherein Q is halo, C_{1-6} alkyl or C_{2-6} alkenyl; X is (a-2) with q and r being O and Z being O, S or SO; R_1 is aryl; R_2 is selected from formyl; C_{1-6}alkyloxycarbonylalkyl; Het[2]; Het[2]C_{1-6}alkyl, C_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from hydroxy, and halo; R_3 is selected from formyl; C_{1-6}alkyl optionally substituted with one or two C_{1-6}alkyloxy; R_4 is hydrogen, with HIV inhibiting properties.

Pyridinone and pyridinethione derivatives having HIV inhibiting properties

The present invention is concerned with pyridinone and pyridinethione derivatives having Human Immunodeficiency Virus (HIV) replication inhibiting properties. It further relates to processes for their preparation and pharmaceutical compositions comprising them. The invention also relates to the use of said compounds in the manufacture of a medicament useful for the treatment of subjects suffering from HIV infection.

Compounds structurally related to the present compounds are disclosed in the prior art.

Naturforsch. B, Anorg. Chem., Org. Chem., 1983, 38 B (3), 398-403 discloses iodine, nitrogen and sulfurylides of 2-pyridones.

Pol. J. Chem., 1979, 53 (11), 2349-2354 discloses N-(tetrahalo-4-pyridyl) aminobenzoic acid derivatives and their use as herbicides.

J. Med. Chem., 1983, 26 (9), 1329-1333 discloses the synthesis of aza analogs of lucanthone useful as antitumor and bactericidal agents.

WO 86/01815 discloses the synthesis of monoazodyes and their use as dyestuffs.

Can. J. Chem., 1980, 58 (5), 501-526 discloses the chemistry of aurodox and related antibiotics.

WO 97/05113 discloses 4-aryl-thio-pyridin-2(1H)-ones and their use for treating HIV related diseases.

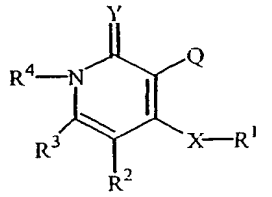
WO 99/55676 discloses 3-(amino- or aminoalkyl)pyridinone or pyridinethione derivatives and their use for the treatment of HIV related diseases.

However their activities are still moderate and their use in human therapy also could lead to the emergence of resistant strains. The most active thiopyridinones disclosed in WO 97/05113 have a 50% inhibitory concentration of virus multiplication (IC_{50}) for nevirapine resistant strains of about 260 nM, whereas the free amino or aminoalkyl pyridinone and pyridinone derivatives disclosed in WO 99/55676 have a

50% inhibitory concentration of virus multiplication for nevirapine resistant strains of more than 10 000 nM.

The Inventors have found a new family of pyridinones and pyridinethiones derivatives which show better HIV inhibitory properties.

The present invention is concerned with compounds of formula



(I),

the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and stereochemically isomeric forms thereof, wherein

Y is O or S;

Q is hydrogen; halo; C_{1-6}alkyl; di(C_{1-4}alkyl)amino; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkylthioC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-S(=O)-; C_{1-6}alkyl-S(=O)$_2$-; hydroxyC_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkylthio; aminocarbonyl$_6C_{1-6}$alkylthio; C_{1-6}alkyloxyC_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, -COOH, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{3-6}cycloalkyl optionally substituted with C_{1-4}alkyl; cyano; carboxyl; formyl; R^5R^6N-C(=O)-; R^5R^6N-C(=O)-C_{1-6}alkyl; *N*-hydroxy-imino; *N*-C_{1-4}alkyloxy-imino; aryl; aryloxy; arylthio; arylC_{1-6}alkyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with hydroxy or aryl; Het^1; Het^{1}oxy; Het^{1}thio; Het$^1C_{1-6}$alkyl; Het^{1}carbonyl; Het$^1C_{1-6}$alkyloxycarbonyl; C_{1-6}alkyl-P(OR^{15})$_2$=O or C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O;

X is a bivalent radical of formula

$-(CH_2)_p-$ (a-1) or

$-(CH_2)_q-Z-(CH_2)_r-$ (a-2);

wherein p is an integer of value 1 to 5;

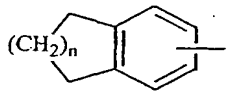
q is an integer of value 0 to 5;

r is an integer of value 0 to 5;

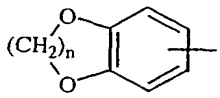
Z is O, S, NR^7, C(=O), S(=O), $S(=O)_2$, $CHOR^{13}$, CH=CH, $CH(NR^7R^8)$ or CF_2;

and wherein each hydrogen atom may be replaced by C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, aryl or a monocyclic or bicyclic heterocycle selected from pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, or a radical of formula


(b-1)

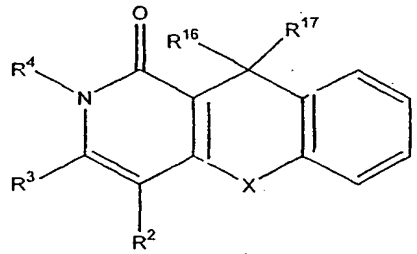
or


(b-2)

with n being an integer of 1 or 2,

said monocyclic or bicyclic heterocycle or said radical of formula (b-1) or (b-2) optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, polyhaloC_{1-4}alkyl or phenyl;

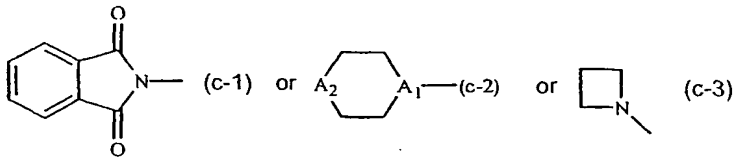
or Q and X-R^1 may be taken together with the pyridinone to form a tricyclic heterocycle of formula


(h-1)

with R^{16} and R^{17} being C_{1-6}alkyl or forming together =O.

R^2 and R^3 each independently are selected from hydrogen; halo; formyl; cyano; azido; hydroxy; oxiranyl; amino; mono- or di(C_{1-4}alkyl)amino; formylamino; mercapto(C_{1-6})alkyl; hydrazino; $R^{5a}R^{6a}N$-C(=O)-; R^9-N=C(R^{10})-; C_{2-6}alkenyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl,

C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, di(C_{1-4}alkyl)carbamoyl, [di(C_{1-4}alkyl)amino(C_{1-6}alkyl)](C_{1-4}alkyl)carbamoyl, [di(C_{1-4}alkyl)amino(C_{1-6}alkyl)](arylC_{1-4}alkyl)carbamoyl, di(C_{1-4}alkyloxy)(C_{1-4}alkyl)carbamoyl, (cyanoC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N*-hydroxy-imino, aryl, Het^2, Het^2carboxamido, Het^2(C_{1-6}alkyl)carbamoyl; C_{2-6}alkynyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{1-6}alkyloxy; hydroxyC_{1-6}alkyloxy; aminoC_{1-6}alkyloxy; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; arylcarbonyl; Het^2carbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxy; aryl; aryloxy; arylC_{1-6}alkyloxy; arylthio; arylC_{1-6}alkylthio; mono- or di(aryl)amino; Het^2; Het^2oxy; Het^2thio; Het^2C_{1-6}alkyloxy; Het^2C_{1-6}alkylthio; Het^2SO_2; Het^2SO; mono- or di(Het^2)amino; C_{3-6}cycloalkyl; C_{3-6}cycloalkyloxy; C_{3-6}cycloalkylthio; C_{1-6}alkylthio; hydroxyC_{1-6}alkylthio; aminoC_{1-6}alkylthio; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, carboxyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl, C_{1-6}alkycarbamoylC_{1-4}alkylthio, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylthio C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, aminocarbonyloxy, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonylC_{1-6}alkylthio, aryl, Het^2, aryloxy, arylthio, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, Het^2C_{1-6}alkyloxy, Het^2C_{1-6}alkylthio, C_{1-6}alkyl-S(=O)$_2$-oxy, amino, mono- or di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkylthio, [di(C_{1-6}alkyl)amino(C_{1-6}alkyl)](C_{1-6}alkyl)amino, di(cyanoC_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, C_{1-6}alkyloxyC_{1-6}alkylcarbonylamino, mono- or di(aryl)amino, mono- or di(arylC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyloxyC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkylthioC_{1-4}alkyl)amino, mono- or di(Het^2C_{1-4}alkyl)amino, (Het^2C_{1-4}alkyl)(C_{1-4}alkyl)amino, (cyanoC_{1-6}alkyl)(C_{1-6}alkyl)amino, C_{3-6}cycloalkylthio, R^{11}-(C=O)-NH-, R^{12}-NH-(C=O)-NH-, R^{14}-S(=O)$_2$-NH-, C_{1-6}alkyl-P(O-R^{15})2=O, C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O or a radical of formula



with A_1 being CH or N, and A_2 being CH_2, NR^{13}, S or O, provided that when A_1 is CH then A_2 is other than CH_2, said radical (c-1), (c-2) and (c-3) being optionally substituted with one or two substituents each independently selected from H, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6} alkyloxycarbonylC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylcarbonyl, arylcarbonyl, aryl, Het^1, Het^1-(C=O)-, hydroxy, cyano, C_{1-4}alkylcyano, $CONR^{16}R^{17}$ with R^{16} and R^{17} being independently H or alkyl, mono or di(C_{1-4}alkyl)aminoalkyl, 4-hydroxy-4-phenyl or 4-cyano-4-phenyl;

or R^2 and R^3 may be taken together to form a bivalent radical of formula

$-(CH_2)_t-CH_2-A_3-CH_2-$ (d-1) or $-CH=CH-CH=CH-$ (d-2)

with t being an integer of 0, 1 or 2 and A_3 being CH_2, O, S, NR^{7a} or $N[C(=O)R^{8a}]$ and wherein each hydrogen in said formula (d-1) or (d-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

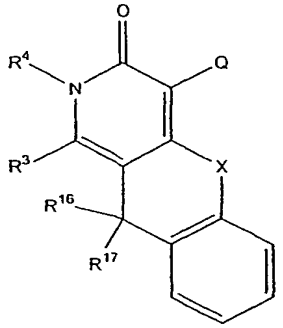
R^4 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, amino, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl or aryl;

or R^4 and R^3 may be taken together to form a bivalent radical of formula

$-(CH_2)_t-CH_2-A_4-CH_2-$ (e-1) or $-CH=CH-CH=CH-$ (e-2)

with t being an integer of 0, 1 or 2 and A_4 being CH_2, O, S, NR^{7b} or $N[C(=O)R^{8b}]$ and wherein each hydrogen in said formula (e-1) or (e-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

or X-R^1 and R^2 may be taken together to form a tricyclic heterocycle of formula

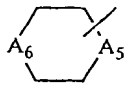


(h-2)

with R^{16} and R^{17} being C_{1-6}alkyl or forming together =O .

R^5 and R^6 each independently are hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^{5a} and R^{6a} each independently are hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkylthio, amino, mono-or di(C_{1-4}alkyl)amino or a radical of formula



(f-1)

with A_5 and A_6 each independently being CH_2, NR^{13} or O;

R^7, R^{7a} and R^{7b} each independently are hydrogen, formyl or C_{1-4}alkyl;

R^8, R^{8a} and R^{8b} each independently are hydrogen or C_{1-4}alkyl;

R^9 is hydrogen, hydroxy, C_{1-4}alkyloxy, carboxylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy or arylC_{1-4}alkyloxy;

R^{10} is hydrogen, carboxyl or C_{1-4}alkyl;

R^{11} is hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkyl-$S(=O)_2$-, aryl or Het^3; C_{1-4}alkyloxy; C_{2-4}alkenyl; arylC_{2-4}alkenyl; Het^3C_{2-4}alkenyl; C_{2-4}alkynyl; Het^3C_{2-4}alkynyl, arylC_{2-4}alkynyl; C_{3-6}cycloalkyl; aryl; naphthyl or Het^3;

R^{12} is C_{1-4}alkyl, arylC_{1-4}alkyl, aryl, arylcarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkyloxycarbonylC_{1-4}alkyl;

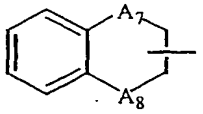
R^{13} is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

R^{14} is C_{1-4}alkyl optionally substituted with aryl or Het^4; polyhaloC_{1-4}alkyl or C_{2-4}alkenyl optionally substituted with aryl or Het^4;

R^{15} is C_{1-4} alkyl;

Het^1 and Het^2 each independently are a heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyrimidinyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl, morpholinyl, thiomorpholinyl triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, indolyl, indazolyl, benzodioxanyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, imidazopyridinyl, dihydropyrrolyl or dihydroisoxazolyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from O, S, halo, formyl, amino, hydroxy, cyano, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, carbamoylC_{1-4}alkyl, carbamoylC_{1-4}alkoxy, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, -$OCONH_2$, C_{1-4}alkoxyC_{1-4}alkyl, aryl, Het^2C_{1-4}alkyl , polyhaloC_{1-4}alkyl, C_{3-6}cycloalkyl or arylC_{2-6}alkenyl,

Het^3 is a monocyclic or bicyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl or a radical of formula



(g-1),

with A_7 or A_8 each independently being selected from CH_2 or O;

each of said monocyclic or bicyclic heterocycles may optionally be substituted with one, two or three substituents each independently selected from halo, hydroxy,C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^4 is a monocyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^5 is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, piperidinyl, morpholinyl or pyrrolidinyl;

aryl is phenyl optionally substituted with one, two or three substituents each independently selected from halo; hydroxy; carboxyl; cyano; formyl; acetyl; nitro; amino; mono- or di(C_{1-4}alkyl)amino; C_{1-4}alkylcarbonylamino; mono- or di(C_{1-4}alkyl)aminocarbonylamino; C_{1-4}alkyl-S(=O)$_2$-NH-; Het^5(=S)-S-C_{1-4}alkyl ; C_{1-6}alkyloxy; sulfamoyl; (C_{1-4}alkyl)sulfamoyl; arylsulfamoyl; Het^2sulfamoyl; O-P=OR^{15}; C_{1-6}alkyl optionally substituted with halo, hydroxy, cyano, nitro, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{2-6}alkenyloxy, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonylthio, *N*-hydroxyimino, phenyl or Het^5; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, nitro, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; phenyl; phenyloxy; phenyl(C_{1-4}alkyl)thioC_{1-4}alkyl; (C_{3-6})cyclohexylthioC_{1-4}alkyl or isoxazolinyl optionally substituted by C_{1-4}alkyloxycarbonyl or morpholinylC_{1-4}alkyl

provided that

5,6,7,8-tetrahydro-3-iodo-4-phenoxy-1-phenyl-2(1*H*)quinolinone;

3-iodo-6-methyl-4-phenoxy-2(1*H*)-pyridinone;

2-[(3,5,6-trifluoro-1,2-dihydro-2-oxo-4-pyridinyl)amino]benzoic acid;

1,2-dihydro-6-hydroxy-2-oxo-4-(2-phenylethyl)-3-pyridinecarbonitrile;

1,2-dihydro-6-hydroxy-2-oxo-4-(4-pyridinylmethyl)-3-pyridinecarbonitrile;
4-[(4-bromophenyl)methoxy]-3,5-diodo-1-methyl-2(1*H*)-pyridinone;
4-[(4-bromophenyl)methoxy]-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxylic acid; 1,2-dihydro-6-methyl-2-oxo-4-(phenylthio)-3-pyridinecarboxylic acid and the alkyl-4-arylthio-1,2-dihydro-5-methyl-6-methyl-2-oxo-3-pyridine carboxylate
3-bromo-4-[[[2-(3,4-dimethoxyphenyl)ethyl]amino]methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-1-methyl-4-phenoxy-2(1*H*)quinolinone;
1-ethyl-3-iodo-7-methoxy-4-phenoxy-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-(4-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
1-ethyl-3-iodo-7-methoxy-4-(4-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-(3-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
1-ethyl-3-iodo-7-methoxy-4-(3-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-phenoxy-2(1*H*)quinolinone;
4-(3-chloro-4-methoxyphenoxy)-3-iodo-7-methoxy-2(1*H*)quinolinone;
3-iodo-4-phenoxy-2(1*H*)quinolinone;
3-iodo-4-phenoxy-1-phenyl-2(1*H*)quinolinone;
3-iodo-4-(4-methylphenoxy)-2(1*H*)quinolinone;
3-iodo-4-(4-methoxyphenoxy)-2(1*H*)quinolinone;
are not included.

As used herein C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylpropyl, 2-methylbutyl and the like; C_{2-4}alkenyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 2 to 4 carbon atoms and containing a double bond such as ethenyl, propenyl, butenyl and the like; C_{2-6}alkenyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 2 to 6 carbon atoms and containing at least one double bond such as the groups defined for C_{2-4}alkenyl and pentenyl, hexenyl, 2,4-hexadienyl, 1,3-butadienyl, 3-methylbutenyl and the like; C_{2-4}alkynyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 2 to 4 carbon atoms and containing one triple bond such as ethynyl, propynyl, butynyl and the like; C_{2-6}alkynyl as a group or part of a group defines straight or branched chain hydrocarbon radicals having from 2 to 6 carbon atoms and containing

one triple bond such as the groups defined such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, 3-methylbutynyl and the like; C_{3-6}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used hereinbefore, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom, a sulfonyl moiety when two of said terms are attached to a sulfur atom, a phosphonate when attached to a phosphorus atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalomethyl as a group or part of a group is defined as mono- or polyhalosubstituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl; polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, for example, the groups defined in halomethyl, 1,1-difluoro-ethyl and the like. In case more than one halogen atom is attached to an alkyl group within the definition of polyhalomethyl or polyhaloC_{1-6}alkyl, they may be the same or different.

The R^1 or Het^1, Het^2, Het^3, Het^4 or Het^5 radical as described above for the compounds of formula (I) may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. For example, when Het^1 is pyridyl, it may be 2-pyridyl, 3-pyridyl or 4-pyridyl.

Lines drawn into ring systems indicate that the bond may be attached to any suitable ring atom.

When any variable (e.g. aryl) occurs more than one time in any constituent, each definition is independent.

It will be appreciated that some of the compounds of formula (I) and their *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used herein before defines all the possible stereoisomeric forms which the compounds of formula (I), and their *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of

compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their *N*-oxides, salts, solvates, quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. In particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not, are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic) malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzensulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate

organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, thiehylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Conversely the salt forms can be converted by treatment with acid into the free acid form.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen.

Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" or "compounds of formula (I-a)" is meant to include also the N-oxides, the addition salts, the quaternary amines and all stereoisomeric forms.

A special group of compound contains those compounds of formula (I) wherein

Q is halo; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkylthioC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl C_{1-6}alkyl-S(=O)-; C_{1-6}alkyl-S(=O)$_2$-; hydroxyC_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{3-6}cycloalkyl optionally substituted with C_{1-4}alkyl; cyano; carboxyl; formyl; R^5R^6N-C(=O)-; R^5R^6N-C(=O)-C_{1-6}alkyl; *N*-hydroxy-imino; *N*-C_{1-4}alkyloxy-imino; aryl; aryloxy; arylthio; arylC_{1-6}alkyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryl; Het^1; Het^1oxy; Het^1thio; Het^1C_{1-6}alkyl; Het^1carbonyl; Het^1C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-P(OR^{15})$_2$=O or C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O

X is a bivalent radical of formula

$-(CH_2)_p-$ (a-1) or

$-(CH_2)_q-Z-(CH_2)_r-$ (a-2);

wherein p is an integer of value 1 to 5;

q is an integer of value 0 to 5;

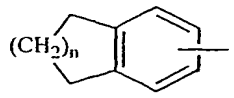
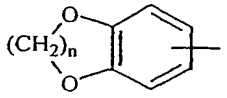
r is an integer of value 0 to 5;

Z is O, S, NR^7, C(=O), S(=O), S(=O)$_2$, $CHOR^{13}$, CH=CH, $CH(NR^7R^8)$ or CF_2;

and wherein each hydrogen atom may be replaced by C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

R^1 is C_{3-6}cycloalkyl, aryl or a monocyclic or bicyclic heterocycle selected from pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl,

imidazolyl, thiazolyl, oxazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, or a radical of formula

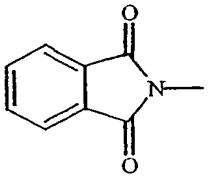
 (b-1) or  (b-2)

with n being an integer of 1 or 2,

said monocyclic or bicyclic heterocycle or said radical of formula (b-1) or (b-2) optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, polyhaloC_{1-4}alkyl or phenyl;

R^2 and R^3 each independently are selected from hydrogen; halo; formyl; cyano; azido; hydroxy; oxiranyl; amino; mono- or di(C_{1-4}alkyl)amino; formylamino; $R^{5a}R^{6a}N$-C(=O)-; R^9-N=C(R^{10})-; C_{2-6}alkenyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{2-6}alkynyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{1-6}alkyloxy; hydroxyC_{1-6}alkyloxy; aminoC_{1-6}alkyloxy; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; arylcarbonyl; Het^2carbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxy; aryl; aryloxy; arylC_{1-6}alkyloxy; arylthio; arylC_{1-6}alkylthio; mono- or di(aryl)amino; Het^2; Het^2oxy; Het^2thio; Het^2C_{1-6}alkyloxy; Het^2C_{1-6}alkylthio; mono- or di(Het^2)amino; C_{3-6}cycloalkyl; C_{3-6}cycloalkyloxy; C_{3-6}cycloalkylthio; C_{1-6}alkylthio; hydroxyC_{1-6}alkylthio; aminoC_{1-6}alkylthio; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyloxy, C_{1-6}alkylthio, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, aminocarbonyloxy, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyloxy, C_{1-6}alkyloxy-carbonylC_{1-6}alkylthio, aryl, Het^2, aryloxy, arylthio, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, Het^2C_{1-6}alkyloxy, Het^2C_{1-6}alkylthio, C_{1-6}alkyl-S(=O)$_2$-oxy, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxy-carbonylamino, C_{1-6}alkyloxyC_{1-6}alkylcarbonylamino, mono- or di(aryl)amino, mono- or di(arylC_{1-}

$_4$alkyl)amino, mono- or di(C_{1-4}alkyloxyC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkylthioC_{1-4}alkyl)amino, mono- or di(Het^2C_{1-4}alkyl)amino, R^{11}-(C=O)-NH-, R^{12}-NH-(C=O)-NH-, R^{14}-S(=O)$_2$-NH-, C_{1-6}alkyl-P(O-R^{15})$_2$=O, C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O or a radical of formula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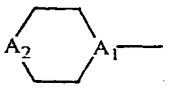
or


(c-2),

with A_1 being CH or N, and A_2 being CH_2, NR^{13}, S or O, provided that when A_1 is CH then A_2 is other than CH_2, said radical (c-1) and (c-2) being optionally substituted with one or two substituents each independently selected from H, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-4}alkyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyloxycarbonylC_{1-4}alkyl, aminoC_{1-6}alkyl, carbonyl, hydroxy, cyano, $CONR^{16}R^{17}$ with R^{16} and R^{17} being independently H or alkyl, mono or di(C_{1-4}alkyl)aminoalkyl, 4-hydroxy-4-phenyl or 4-cyano-4-phenyl;

or R^2 and R^3 may be taken together to form a bivalent radical of formula

$$-(CH_2)_t-CH_2-A_3-CH_2- \text{ (d-1)} \qquad \text{or} \qquad -CH=CH-CH=CH- \text{ (d-2)}$$

with t being an integer of 0, 1 or 2 and A_3 being CH_2, O, S, NR^{7a} or N[C(=O)R^{8a}] and wherein each hydrogen in said formula (d-1) or (d-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^4 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, amino, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl or aryl;

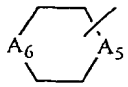
or R^4 and R^3 may be taken together to form a bivalent radical of formula

$$-(CH_2)_t-CH_2-A_4-CH_2- \text{ (e-1)} \qquad \text{or} \qquad -CH=CH-CH=CH- \text{ (e-2)}$$

with t being an integer of 0, 1 or 2 and A_4 being CH_2, O, S, NR^{7b} or N[C(=O)R^{8b}] and wherein each hydrogen in said formula (e-1) or (e-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^5 and R^6 each independently are hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^{5a} and R^{6a} each independently are hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkylthio, amino, mono- or di(C_{1-4}alkyl)amino; or a radical of formula



(f-1)

with A_5 and A_6 each independently being CH_2, NR^{13} or O;

R^7, R^{7a} and R^{7b} each independently are hydrogen, formyl or C_{1-4}alkyl;

R^8, R^{8a} and R^{8b} each independently are hydrogen or C_{1-4}alkyl;

R^9 is hydrogen, hydroxy, C_{1-4}alkyloxy, carboxylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy or arylC_{1-4}alkyloxy;

R^{10} is hydrogen, carboxyl or C_{1-4}alkyl;

R^{11} is hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkyl-$S(=O)_2$-, aryl or Het^3; C_{1-4}alkyloxy; C_{2-4}alkenyl; arylC_{2-4}alkenyl; Het^3C_{2-4}alkenyl; C_{2-4}alkynyl; Het^3C_{2-4}alkynyl, arylC_{2-4}alkynyl; C_{3-6}cycloalkyl; aryl; naphthyl or Het^3;

R^{12} is C_{1-4}alkyl, arylC_{1-4}alkyl, aryl, arylcarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, or C_{1-4}alkyloxycarbonylC_{1-4}alkyl;

R^{13} is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

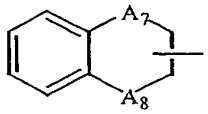
R^{14} is C_{1-4}alkyl optionally substituted with aryl or Het^4; polyhaloC_{1-4}alkyl or C_{2-4}alkenyl optionally substituted with aryl or Het^4;

R^{15} is C_{1-4}alkyl;

Het^1 and Het^2 each independently are a heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl,

hexahydropyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl or 2-oxo-1,2-dihydro-quinolinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^3 is a monocyclic or bicyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl or a radical of formula



(g-1),

with A_7 or A_8 each independently being selected from CH_2 or O;

each of said monocyclic or bicyclic heterocycles may optionally be substituted with one, two or three substituents each independently selected from halo, hydroxy,C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^4 is a monocyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^5 is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl or oxazolyl;

aryl is phenyl optionally substituted with one, two or three substituents each independently selected from halo; hydroxy; carboxyl; cyano; formyl; nitro; amino; mono- or di(C_{1-4}alkyl)amino; C_{1-4}alkylcarbonylamino; mono- or di(C_{1-4}alkyl)aminocarbonylamino; C_{1-4}alkyl-S(=O)$_2$-NH-; C_{1-6}alkyloxy; C_{1-6}alkyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy,

C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; phenyl or phenyloxy;

A special group of compound contains those compounds of formula (I) wherein

Q is halo, C_{1-6}alkyl or C_{2-6}alkenyl;

X is (a-2) with q and r being 0 and Z being O, S or SO;

R_1 is aryl;

R_2 is selected from formyl; C_{1-6}alkyloxycarbonylalkyl; Het^2; Het^2C_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from hydroxy or halo;

R_3 is selected from formyl; C_{1-6}alkyl optionally substituted with one or two C_{1-6}alkyloxy;

R_4 is hydrogen.

Particular compounds are those compounds of formula (I) wherein Q is iodo.

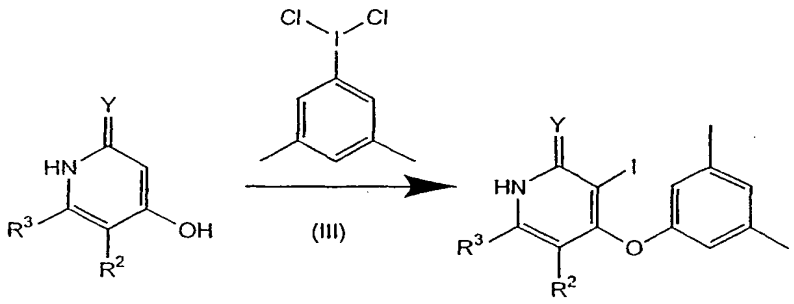
Preferred compounds are those compounds of formula (I) wherein Q is iodo, X-R_1 is a 3,5-dimethylphenylthio or a 3,5-dimethylphenyloxy and R_2 is a hydroxymethyl or a N-morpholinomethyl or a 3-phenylpropyl or a furan-2-yl-methylthiomethyl. Also preferred compounds are those compounds of formula (I) wherein Q is iodo, X-R_1 is a 3-(2-cyano-vinyl)-5-iodophenyloxy or 5-bromo-3-(2-cyano-vinyl) and R_2 is ethyl.

Most preferred compounds are compounds n° 242, 255, 43, 264, 124, 249, 298, 326, 133, 241, 253, 306, 328, 46, 105, 234, 254, 256, 272, 284, 296, 319, 83, 88, 108, 109, 115, 277, 286, 299, 45, 85, 86, 231, 244, 297, 250, 257, 307, 324, 81, 92, 140, 143, 217, 221, 230, 232, 245, 309; 321, 322, 31, 218, 222, 314, 8, 99, 121, 219, 233, 280, 551, 470, 375, 483, 547, 606, 618, 662, 694, 700, 709 and 713 of table 1.

The present invention also relates to a method of treating warm-blooded animals suffering from HIV infection. Said method comprises the administration of the therapeutically effective amount of a compound of formula (I) or any sub group thereof, a *N*-oxide form, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

The compounds of formula (I) can be prepared according to art-known procedures.

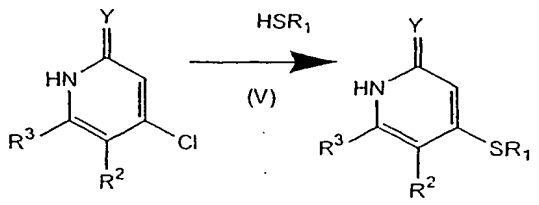
In general, compounds of formula (I) wherein X is an oxygen and R_1 a 3,5-dimethylphenyl, said compound being represented by formula (I-a) can be prepared by reacting an intermediate of formula (II) with a derivative of formula (III)



(II) (I-a)

In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

The compounds of formula (I) wherein X is a sulphur, said compound being represented by formula (I-b) can be prepared by reacting an intermediate of formula (IV) with a derivative of formula (V) in an appropriate solvent such as for example methanol, ethanol, propanol, butanol, dioxane, tetrahydrofurane, 2-methoxyethylether or toluene, and the like. This reaction can be performed at a temperature comprised between 20 and 130°C.



(IV) (I-b)

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. t.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said

mixtures of diastereomeric salts or compounds by, for example, selective crystallization of chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures.

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized as a mixture of stereoisomeric forms, in particular in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include tert-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C_{1-6}alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in '*Protective Groups in Organic Chemistry*', edited by J W F McOmie, Plenum Press (1973), and '*Protective Groups in Organic Synthesis*' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

The compounds of the present invention show antiretroviral properties, in particular against Human Immunodeficiency Virus (HIV), which is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an everdecreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to combat infections and neoplasms and the HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers. Other conditions associated with HIV infection include thrombocytopaenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as progressive dysarthria, ataxia and disorientation. HIV

infection further has also been associated with peripheral neuropathy progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).

The present compounds also show activity against HIV-1 strains that have acquired resistance to art-know non-nucleoside reverse transcriptase inhibitors. They also have little or no binding affinity to human α-1 acid glycoprotein.

Due to their antiretroviral properties, particularly their anti-HIV properties, especially their anti-HIV-1-activity, the compounds of the present invention are useful in the treatment of individuals infected by HIV and for the prophylaxis of these individuals. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses whose existence is mediated by, or depends upon, the enzyme reverse transcriptase. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic CNS diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically

acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid sugars, kaolin, lubricants, binders, disintegrating agent and the like in the case of powders pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the list advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

To aid solubility of the compounds of formula (I), suitable ingredients, e.g. cyclodextrins, may be included in the compositions. Appropriate cyclodextrins are α, β, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD;

hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxy-propyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxy-ethyl; C_{1-6}alkylcarbonyl, particularly acetyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxypropyl-β-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The M.S. and D.S. value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. Preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10 and the D.S. ranges from 0.125 to 3.

Other suitable compositions for oral or rectal administration comprise particles obtainable by melt-extruding a mixture comprising a compound of formula (I) and an appropriate water-soluble polymer and subsequently milling said melt-extruded mixture. Said particles can then be formulated by conventional techniques into pharmaceutical dosage forms such as tablets and capsules.

Said particles consist of a solid dispersion comprising a compound of formula (I) and one or more pharmaceutically acceptable water-soluble polymers. The preferred technique for preparing solid dispersions is the melt-extrusion process comprising the following steps :

a) mixing a compound of formula (I) and an appropriate water-soluble polymer,

b) optionally blending additives with the thus obtained mixture,

c) heating the thus obtained blend until one obtains a homogenous melt,

d) forcing the thus obtained melt through one or more nozzles; and

e) cooling the melt till it solidifies.

The solid dispersion product is milled or ground to particles having a particle size of less than 1500 μm, preferably less than 400 μm, more preferably less than 250 μm and most preferably less than 125 μm.

The water-soluble polymers in the particles are polymers that have an apparent viscosity, when dissolved at 20°C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa.s, more preferably of 1 to 700 mPa.s, and most preferred of 1 to 100 mPa.s. For example, suitable water-soluble polymers include alkylcelluloses, hydroxyalkylcelluloses, hydroxyalkyl alkylcelluloses, carboxyalkylcelluloses, alkali metal salts of carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters, starches, pectines, chitin derivates, polysaccharides, polyacrylic acids and the salts thereof, polymethacrylic acids and the salts and esters thereof, methacrylate copolymers, polyvinylalcohol, polyalkylene oxides and copolymers of ethylene oxide and propylene oxide. Preferred water-soluble polymers are Eudragit E® (Röhm GmbH, Germany) and hydroxypropyl methylcelluloses.

Also one or more cyclodextrins can be used as water soluble polymer in the preparation of the above-mentioned particles as is disclosed in WO 97/18839. Said cyclodextrins include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α, β, γ-cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used include polyethers described in U.S. Patent 3,459,731. Further substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl,

hydroxyC_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonylC_{1-6}alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxyC_{2-4}alkyl or carboxyC_{1-2}alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

Of particular utility are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described by M. Nogradi (*Drugs of the Future*, (1984) Vol. 9, No. 8, p. 577-578) and polyethers, e.g. hydroxypropyl β-cyclodextrin and hydroxyethyl β-cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin an propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

A more novel type of substituted cyclodextrins is sulfobutylcyclodextrines.

The ratio of the compound of formula (I) over cyclodextrin may vary widely. For example ratios of 1/100 to 100/1 may be applied. Interesting ratios of the compound of formula (I) over cyclodextrin range from about 1/10 to 10/1. More interesting ratios range from about 1/5 to 5/1.

It may further be convenient to formulate the compounds of formula (I) in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the compound of formula (I) but do not chemically bond to said compound.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low

molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds of formula (I) involves a pharmaceutical composition whereby the compounds of formula (I) are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

Said beads comprise a central, rounded or spherical core, a coating film of a hydrophilic polymer and a compound of formula (I) and a seal-coating polymer layer.

Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results presented here. In general, it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to

administer the required dose at two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg , and in particular 5 to 200 mg of active ingredient per unit dosage form.

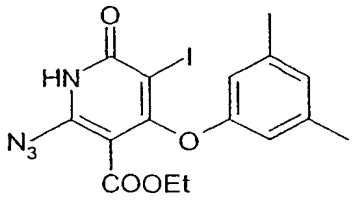
The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, the weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased of the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

Also, the combination of an antiretroviral compound and a compound of the present invention can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of the present invention, and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. Said other antiretroviral compounds may be known antiretroviral compounds such as nucleoside reverse transcriptase inhibitors, e.g. zidovudine (3'-azido-3'-deoxythymidine; AZT), didanosine (dideoxy inosine; ddI), zalcitabine (dideoxycytidine; ddC) or lamivudine (3'-thia-2'-3'-dideoxycytidine; 3TC) and the like; non-nucleoside reverse transcriptase inhibitors such as suramine, pentamidine, thymopentin, castanospermine, efavirenz, rescriptor (BHAP derivative), dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate), nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6*H*dipyrido[3,2-b: 2',3'-e][1,4]diazepin-6-one), tacrine (tetrahydroaminoacridine) and the like; compounds of the TIBO (tetrahydro-

imidazo[4,5,1-jk][1,4]-benzodiazepine-2(1*H*)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo-[4,5,1-jk][1,4]benzodiazepine-2(1*H*)-thione compounds of the α-APA (α-anilino phenyl acetamide) type e.g. α-[(2-nitro-phenyl)amino]-2,6-dichloro-benzene-acetamide and the like; TAT-inhibitors, e.g. RO-5-3335 and the like; protease inhibitors e.g. indinavir, ritanovir, saquinovir, ABT-378 and the like; fusion inhibitors; integrase inhibitors; or immunomodulating agents, e.g. levamisole and the like. The compound of formula (I) can also be combined with another compound of formula (I).

The following examples are intended to illustrate the present invention. The numbers under the formulas correspond to the numbers in the table (I).

Example 1 : Ethyl 2-azido-4-(3,5-dimethylphenoxy)- 1,6-dihydro- 5-iodo-6-oxo-3 – pyridinecarboxylate (compound 106)



106

2-chloro-4-hydroxy-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid ethyl ester (intermediate 1) was obtained as described by J. A. Elvidge and N. A. Zaidi (*J. Chem. Soc.*, (1968), **17**, 2188) and dichloro-3,5-dimethyliodobenzene (intermediate 2) as described by H.J. Lucas, E.R. Kennedy, Org. Synth. (1955) **Vol-III**, 482-483.

1.1.: Ethyl 2-chloro-4-(3,5-dimethylphenoxy)-1,6-dihydro-5-iodo-6-oxo-3-pyridinecarboxylate (intermediate 3)

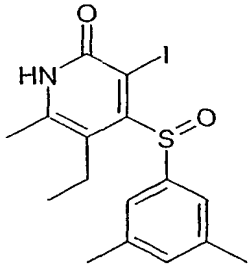
Intermediate 2 (0.73 g, 2.2 mmol) was suspended in 10 ml of water containing sodium carbonate (0.24 g, 2.2 mmol) and stirred for 30 min. at room temperature. To this mixture a solution of intermediate 1 (0.44 g, 2 mmol) in 10 ml of water containing also sodium carbonate (0.22 g; 2 mmol) was added. After stirring for one hour at 20°C the precipitate was filtered off, washed with water, dried *in*

vacuo and suspended in diglyme (5 ml). After heating at 100°C for 10 min., the solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/ethanol 98:2) gave the titled compound (0.6 g, 67%) as yellow microcrystals, m. p. 180-182°C

1.2.: Ethyl 2-azido-4-(3,5-dimethylphenoxy)-1,6-dihydro-5-iodo-6-oxo-3-pyridinecarboxylate (compound 106)

Sodium azide (0.20 g, 3.12 mmol) was added to a solution of intermediate 3 (0.50 g, 1.56 mmol) in DMSO (5ml), and the mixture was heated at 50°C for 5 hours Reaction mixture was partitioned between water (30 ml) and ethyl acetate (40 ml). The organic layer was dried over magnesium sulfate and concentred. Flash chromatography (SiO_2, CH_2Cl_2/ethanol 95:5) gave the desired product (0.49 g, 70%) as a white solid, m. p. = 216-218°C.

Example 2: 4-[3,5-dimethylphenyl)-sulfinyl]-5-ethyl-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 108)



108

4-[3,5-dimethylphenyl)-thio]-5-ethyl-6-methyl-2(1*H*)-pyridinone (intermediate 4) was obtained as described by Dollé *et al.* (*J. Med. Chem.*, (1995), **38**, 4679-4686).

2.1.: 4-[3,5-dimethylphenyl)-thio]-5-ethyl-3-iodo-6-methyl-2(1*H*)-pyridinone (intermediate 5)

The intermediate 4 (273 mg; 1 mmol) was dissolved in acetic acid (4 ml) and ethyl acetate (4 ml). At room temperature and in the dark *N*-iodosuccinimide (225 mg ; 1 mmol) was added in one portion. After 4 hours under stirring at room

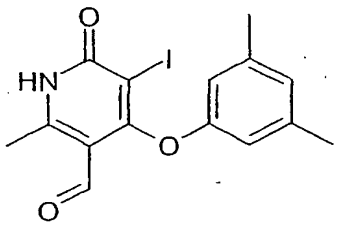
temperature, the mixture was poured into water (15 ml) and the pH of the solution was adjusted to 7 with 28% ammonia. The combined organic layers obtained by extraction with ethyl acetate (3x30 ml) were washed with brine (10 ml), dried over magnesium sulfate and evaporated to give a gum. It was then purified by flash chromatography on silica gel column with CH_2Cl_2-ethanol (98:2) as the eluent to give the main fraction containing the titled compound which was recristallized from ethanol furnishing the pure intermediate 5 as yellow microcrystals (122 mg ; 51%), m. p. = 252°C.

2.2.: 4-[3,5-dimethylphenyl)-sulfinyl]-5-ethyl-3-iodo-6-methyl-2(1H)-pyridinone (compound 108)

m-chloroperbenzoic acid and water (70%, 123 mg ; 0.5 mmol) in chloroform (15 ml) was dried over magnesium sulfate and filtered. To this solution at 0°C was added the intermediate 5 (200 mg ; 0.5 mmol) and the mixture was kept under stirring for 1 hour. A saturated solution of sodium carbonate (5 ml) was added and the combined organic layers obtained by extraction with CH_2Cl_2 (3x30 ml) were dried over magnesium sulfate and evaporated. The residue obtained was then chromatographed (SiO_2, CH_2Cl_2/ethanol 98:2) to give the titled compound (113 mg; 50%).

1H NMR. (200 MHz, CDCl3), d : 0.66 (t, 3H, CH3-CH2, J=6.9 Hz) ; 2.20-2.90 (m, 11H, CH3-6,3',5', CH2CH3); 7.08 (s, 1H, H-4') ; 7.25 (s, 2H, H-2',6') ; 12.9 (s, 1H, NH).

Example 3: 4-(3,5-dimethylphenoxy)-1,6-dihydro-5-iodo-2-methyl-6-oxo–3-pyridinecarboxaldehyde (compound 269)



269

Ethyl 4-hydroxy-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarboxylate (intermediate 6) was described by E. Knoevenagel and A. Fries (*Ber.*, (1898), 31, 768).

3.1.: Ethyl 4-hydroxy-5-hydroxymethyl-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarboxylate (intermediate 7)

The mixture of intermediate 6 (1.8 g; 9.1 mmol), Na_2CO_3 (970 mg ; 9.1 mmol) and water (30 ml) was heated in an oil bath at 90°C. Three portions of 37% formaldehyde solution in water (1.46 ml; 18.2 mmol each) were added every 45 min. The homogeneous mixture obtained was kept at the same temperature for 30 min. further and the oil bath was removed. When the internal temperature reaches 60°C, ethyl acetate (40 ml) and acetic acid (1.8 ml) were added and after extraction with hot ethyl acetate (4x40 ml) the organic layer was evaporated under reduced pressure. The residue was then purified by flash chromatography on a silica gel column with CH_2Cl_2/ethanol (95:5) as the eluent to give the expected intermediate 7 (830 mg; 40%), m. p. = 262-265°C.

3.2.: Ethyl 5-formyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydro-3-pyridine-3-carboxylate (intermediate 8)

To a stirred solution of intermediate 7 (500 mg ; 2.2 mmol) in CH_2Cl_2 (80 ml) was added at reflux MnO_2 (4 g ; 46 mmol) and the reflux was maintained for 50 hours. The hot mixture was filtered off, the solid was washed successively with hot methanol (3x50 ml) and hot ethyl acetate (3x50 ml). The solvents were evaporated and the solid residue obtained was then purified by flash chromatography on a column of silica gel with CH_2Cl_2/ethanol (98:2) as the eluent to give the intermediate 8 (420 mg; 85%); m. p. = 248-250°C.

3.3.: 4-hydroxy-2-methyl-6-oxo-1,6-dihydro-3-pyridinecarboxaldehyde (intermediate 9)

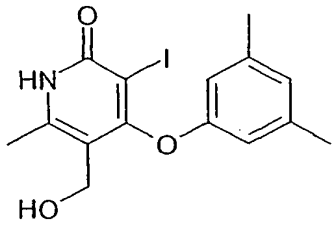
To a solution of intermediate 8 (350 mg ;1.5 mmol) in 1,4-dioxane (15 ml) was added water (7.6 ml) and 1N HCl (2.4 ml) and the mixture was heated under reflux for 24 hours. The hot solution was extracted with ethyl acetate (3x30 ml) and

the solvent was removed under reduced pressure furnishing the titled intermediate 9 as yellow microcrystals (110 mg; 47%); m. p. > 260°C. This compound was used for the next step without any further purification.

3.4.: 4-(3,5-dimethylphenoxy)-1,6-dihydro-5-iodo-2-methyl-6-oxo–3-pyridinecarboxaldehyde (compound 269)

Intermediate 2 (1.31 g, 4.32 mmol) was suspended in 25 ml of water containing sodium carbonate (0.46 g, 4.32 mmol) and stirred for 30 min. at room temperature. To this mixture a solution of intermediate 9 (0.55 g, 3.6 mmol) in 25 ml of water containing also sodium carbonate (0.38 g; 3.6 mmol) was added. After stirring for 1hour at 20°C the precipitate was filtered off, washed with water, dried *in vacuo* and suspended in dimethylformamide (15 ml). After heating under reflux for 1h the solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/EtOH 95:5) gave the titled compound (1.01 g, 73%) as yellow microcrystals, m. p. >260°C.

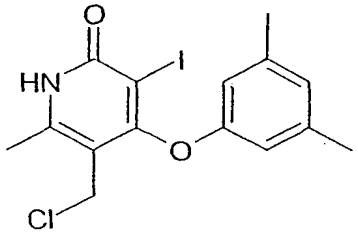
Example 4: 4-(3,5-dimethylphenoxy)-5-(hydroxymethyl)-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 257)



257

To a stirred solution of compound 269 (500 mg ; 1.3 mmol) in methanol (50 ml) was added $NaBH_4$ (350 mg ; 9.2 mmol) in small portions for a period of 10 min. After 1hour on stirring at room temperature, water (20 ml) and a solution 10% potassium carbonate (30 ml) were added. The mixture was extracted with ethyl acetate (3x60 ml) and the organic layer was washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure giving colorless microcrystals which correspond to the titled compound (490 mg ; 97%) m.p.=248-250°C.

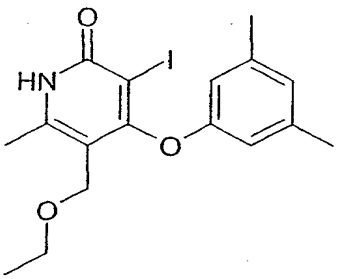
Example 5: 5-(chloromethyl)-4-(3,5-dimethylphenoxy)-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 125)



125

The heterogeneous solution of compound 257 (450 mg; 1.2 mmol) in CH_2Cl_2 (30 ml) became homogeneous mixture by addition at room temperature of $SOCl_2$ (2.6 ml). After 2 hours on stirring at room temperature, all the volatiles were removed under reduced pressure giving a yellow solid which corresponds to the expected compound 125 in quantitative yield (470 mg); m. p.= 256-258°C. This compound was used for the next step without any further purification.

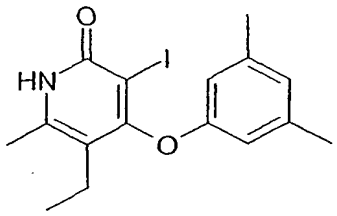
Example 6: 4-(3,5-dimethylphenoxy)-5-(ethoxymethyl)-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 255)



255

A solution of compound 125 (60 mg; 0.15 mmol) in absolute ethanol (5 ml) and potassium carbonate (60 mg; 0.44 mmol) was heated under reflux for 16 hours. After evaporation under reduced pressure, water (5 ml) was added and the mixture was extracted with ethyl acetate (3x10 ml). The organic layer was washed with brine (5 ml), dried over magnesium sulfate and the solvent was removed. The colorless solid residue was then purified by flash chromatography on a silica gel column with CH_2Cl_2/ethanol (98:2) as the eluent to give the titled compound 255 (59 mg; 95%); m. p. = 234-236°C.

Example 7: 4-(3,5-dimethylphenoxy)-5-ethyl-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 258)

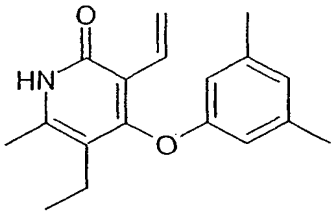


258

This compound was prepared starting from the 5-ethyl-6-methyl-4-hydroxypyridin-2(1*H*)-one (intermediate 10) which was obtained as described by Dollé *et al.* (*J. Med. Chem.*, (1995), **38**, 4679-4686).

Intermediate 2 (3,75 g ; 12,4 mmol) was suspended in water (50 ml) containing sodium carbonate (1,31 g ; 12,4 mmol) and stirred for 30 min at room temperature. To this mixture a solution intermediate 10 (1,9 g; 12,4 mmol) in water (50 ml) containing also sodium carbonate (1,31 g ; 12,4 mmol) was added. After stirring for 1hour at 20°C the precipitate was filtered off, washed with water, dried under vacuum at room temperature and suspended in dimethylformamide (20 ml). The mixture was refluxed for 1hour. The solvent was removed *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/ Et OH 98:2) gave the titled compound (4,3 g; 90%) as colorless microcrystals; m. p. = 240°C.

Example 8: 4-(3,5-dimethylphenoxy)-3-ethenyl-5-ethyl-6-methyl-2(1*H*)-pyridinone (compound 234)

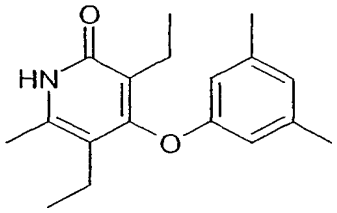


234

Compound 258 (300 mg, 0.1783 mmol) and palladium tetrakistriphenylphosphine (45 mg, 5%mol) were dissolved in toluene (6 ml). Tributyl(vinyl)tin (358 mg, 0.94 mmol) was added at room temperature. The mixture

was refluxed for 12 hours. Water (8 ml) was added and the aqueous layer was extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed under vacuum and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethanol 98:2) to give the titled compound 234 as colorless microcrystals (87 mg, 39%); m. p. = 200°C.

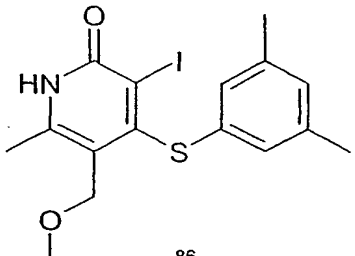
Example 9: 4-(3,5-dimethylphenoxy)-3,5-diethyl-6-methyl-2(1*H*)-pyridinone (compound 231)



231

Compound 234 (90 mg, 0.318 mmol) was dissolved in absolute ethanol (10 ml). The catalyst palladium on carbon 10% (44 mg) was added. The mixture was stirred under hydrogen atmosphere at room temperature for 12hours. The catalyst was filtered off and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/ethanol 98:2) to give the desired compound as colorless microcrystals (60 mg, 66%);, m.p. = 180°C.

Example 10: 4-[3,5-dimethylphenyl)-thio]-5-(ethoxymethyl)-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 86)



86

10.1. Ethyl 4-hydroxy-2-methyl-6-oxo-1,6-dihydro-3-pyridinecarboxylate (intermediate 12)

This compound was prepared starting from the di-(2,4,6-trichlorophenyl)malonate (intermediate 11) which was obtained as described by Kappe, Th., (*Mh. Chem.* (1967), 98, 874).

A solution of ethyl 3-aminocrotonate (12.6 g, 97.5 mmol) and of intermediate 11 in diglyme (400 ml) was heated at 100° C for 3 hours during which the product separated out. After cooling, diethylether (1.5 l) was added and the desired intermediate 12 was filtered (14.2 g, 75%). m. p. 243-245°C.

10.2.: Ethyl 4-chloro-2-methyl-6-oxo-1,6-dihydro-3-pyridinecarboxylate (intermediate 13)

To a solution of intermediate 12 (2 g; 10 mmol) and benzyltriethylammonium chloride (9.1 g; 40 mmol) in acetonitrile (40 ml) was added in one portion phosphorus oxychloride (2.2 ml ; 24 mmol). The obtained mixture was stirred at room temperature under nitrogen atmosphere for 5 min. and heated under reflux for 2hours. After evaporation of the solvent, cool water (40 ml) was added and the mixture was stirred for 0.5hour. Extraction with CH_2Cl_2 followed by a silica gel column chromatography using CH_2Cl_2/ethanol (99:1) as eluent gave i) ethyl 2,4-dichloro-6-methylpyridin-5-ylcarboxylate (1.7 g ; 72%) (which can be transformed into the intermediate 13 and ii) intermediate 13 (506 mg; 24%) m.p.=161-163°C.

10.3.: Ethyl 4-[(3,5-dimethylphenyl)-thio]-1,6-dihydro-2-methyl-6-oxo–3-pyridinecarboxylate (intermediate 14)

A mixture of the intermediate 13 (1.2 g ; 5.6 mmol) in ethanol (15 ml), triethylamine (1.5 ml) and 3,5-dimethylthiophenol (1.45 ml ; 11 mmol) was heated under reflux for 16 hours. After evaporation under reduced pressure, diethylether (50 ml) was added and the precipitate was filtered off. The intermediate 14 was obtained (1.42 g; 80%) as a colorless solid m.p.= 233-235°C.

10.4.: 4-[(3,5-dimethylphenyl)-thio]-5-(hydroxymethyl)-6-methyl-2(1*H*)-pyridinone (intermediate 15)

Under nitrogen atmosphere, the intermediate 14 (500 mg ; 1.6 mmol) was suspended in dry tetrahydrofurane (20 ml) and $LiAlH_4$ (120 mg; 3.2 mmol) was added at 0°C. The mixture was stirred at room temperature for 18 hours and poured in ethyl acetate (50 ml) at 0°C and a solution 10% H_2SO_4 (100 ml) was added dropwise. The mixture was extracted with ethyl acetate (2x100ml) and the organic layer was removed under reduced pressure giving the intermediate 15 (310 mg; 71%) m.p.=268-270°C.

10.5.: 4-[(3,5-dimethylphenyl)-thio]-5-(chloromethyl)-6-methyl-2(1*H*)-pyridinone (intermediate 16)

A suspension of intermediate 15 (275 mg ; 1 mmol) in dichloromethane (10 ml) became homogeneous by addition of $SOCl_2$ (2.3 ml) at room temperature. After 2 hours of stirring at room temperature, all the volatiles were removed under reduced pressure giving a yellow solid which corresponds to the expected intermediate 16 in quantitative yield (294 mg).
This compound was used for the next step without further purification.

10.6.: 4-[(3,5-dimethylphenyl)-thio]-5-(ethoxymethyl)-6-methyl-2(1*H*)-pyridinone (intermediate 17)

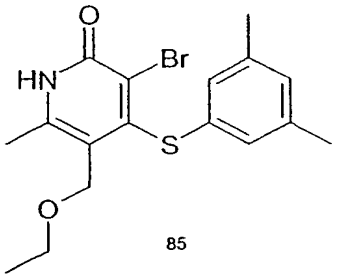
A solution of intermediate 16 (250 mg ; 0.85 mmol) in absolute ethanol (10 ml) and triethylamine (0.24 ml) was heated at 50°C for 18 hours. After evaporation under reduced pressure the residue was purified by flash chromatography on a silica gel column with CH_2Cl_2/ethanol (99:1) as the eluent to give the titled intermediate 17 (243 mg; 94%) m.p. = 203-205°C.

10.7.: 4-[3,5-dimethylphenyl)-thio]-5-(ethoxymethyl)-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 86)

The intermediate 17 (100 mg ; 0.33 mmol) was dissolved in acetic acid (2 ml) and ethyl acetate (2 ml). At room temperature and in the dark *N*-iodosuccinimide (75 mg ; 0.33 mmol) was added in one portion. After 2.5 h under stirring at room temperature, the mixture was poured into water (5 ml) and the pH of the solution was

adjusted to ca.7 with 28% ammonia. The combined organic layers obtained by extraction with CH_2Cl_2 (3x10 ml) were washed with water (15 ml), dried over magnesium sulfate and evaporated to give a solid residue. It was then chromatographed on silica gel column with CH_2Cl_2/ethanol (99:1) as the eluent to give the titled compound 86 as colorless microcrystals (96 mg; 68%) m.p.=220-222°C.

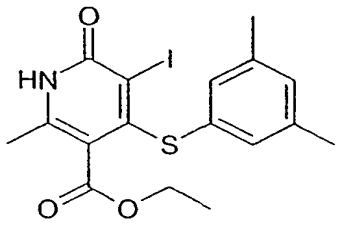
Example 11: 3-bromo-4-[3,5-dimethylphenyl)-thio]- 5-(ethoxymethyl)-6-methyl-2(1*H*)-pyridinone (compound 85)



85

The intermediate 17 (50 mg ; 0.16 mmol) was dissolved in acetic acid (3 ml) and ethyl acetate (3 ml). At room temperature and in the dark *N*-bromosuccinimide (29 mg ; 0.16 mmol) was added in one portion. After 30 min. under stirring at room temperature, the mixture was poured into water (10 ml) and the pH of the solution was adjusted to ca.7 with 28% ammonia. The combined organic layers obtained by extraction with ethyl acetate (3x15 ml) were dried over magnesium sulfate and evaporated to give a solid residue. It was then purified by flash chromatography on silica gel column with CH_2Cl_2/ethanol (99:1) as the eluent to give the titled compound 85 as colorless microcrystals (48 mg; 76%) m.p.= 183-184°C.

Example 12: Ethyl 4-[3,5-dimethylphenyl)-thio]-1,6-dihydro-5-iodo-2-methyl-6-oxo-3-pyridinecarboxylate (compound 71)



71

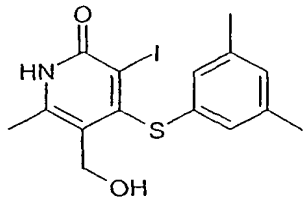
12.1.: Ethyl 4-[3,5-dimethylphenyl)-thio]-1,6-dihydro-2-methyl-6-oxo-3-pyridinecarboxylate (intermediate 18)

3,5-dimethylthiophenol (0.69 ml ; 5.1 mmol) was added to a mixture of intermediate 13 (1 g ; 4.6 mmol) in triethylamine (1 ml) and ethanol (10 ml). The mixture was stirred and refluxed then brought to room temperature and poured out into water. The precipitate was filtered. The residue was crystallized from diethyl ether. The precipitate was filtered off and dried to yield (1,2 g; 80%) of intermediate 18; m.p. = 230°C.

12.2.: Ethyl 4-[3,5-dimethylphenyl)-thio]-1,6-dihydro-5-iodo-2-methyl-6-oxo-3-pyridinecarboxylate (compound 71)

N-iodosuccinimide (0.085 g ; 0.4 mmol) was added at room temperature to a solution of intermediate 18 (0.1. g ; 0.3 mmol) in ethyl acetate (0.3 ml) and acetic acid (0.3 ml) under nitrogen. The mixture was stirred 48 hours in darkness. The solvent was evaporated. The residue was purified by column chromatography over Kromasil® (CH_2Cl_2 ; 100). Two fractions were collected and the solvent was evaporated to give 0.052 g of a compound which was crystallized from diisopropyl ether. The precipitate was filtered off and dried to yield (32 mg; 23%) of compound 71; m.p. = 210°C.

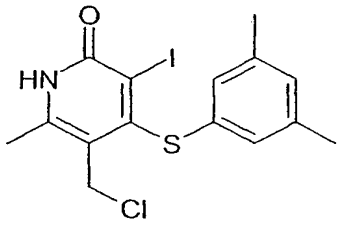
Example 13: 4-[3,5-dimethylphenyl)-thio]-5-(hydroxymethyl)-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 61)



61

Diisobutylaluminium hydride (20wt.% solution in toluene) (0.75 ml; 0.9 mmol) was added at -70°C to a mixture of compound 71 (0.1 g ; 0.2 mmol) in toluene (10 ml). The mixture was stirred at 0°C for 1 hour, poured out into water and extracted with ethyl acetate. The residue was crystallized from diisopropyl ether. The precipitate was filtered off and dried to yield (56 mg; 70%) of compound 61 ; m.p.= 240°C.

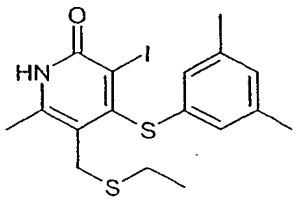
Example 14: 5-(chloromethyl)-4-[3,5-dimethylphenyl)-thio]-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 60)



60

$SOCl_2$ (0.9 ml ; 12.3 mmol) was added dropwise at 0°C to a solution of compound 61 (0.8 g; 1.9 mmol) in CH_2Cl_2 (90 ml). The mixture was stirred at room temperature overnight and evaporated till dryness. The residue was taken up in CH_2Cl_2 and evaporated (3 times) to yield 0.7 g (89 %) m.p. = 218°C. The product was used without further purification in the next reaction step.

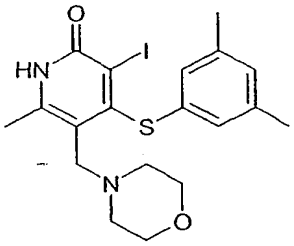
Example 15: 4-[3,5-dimethylphenyl)-thio]-5-[(ethylthio)methyl]-3-iodo-6-methyl-2(1*H*)-pyridinone (compound 45).



45

A mixture of compound 60 (0.1 g ; 0.2 mmol) and ethanethiol (0.036 ml ; 0.5 mmol) in triethylamine (0.1 ml) and ethanol (2 ml) was stirred and refluxed for 4 hours. The solvent was evaporated. The residue (0.06 g) was purified by column chromatography over silica gel (eluent : $CH_2Cl_2/CH_3OH/NH_4OH$; 95/5/0. 1). The pure fractions were collected and the solvent was evaporated. The residue (0.02 g) was crystallized from diisopropylether. The precipitate was filtered off and driedto yield 0.018 g (17 %); m.p.= 210°C.

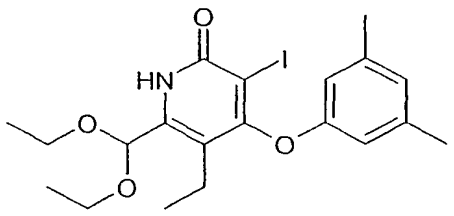
Example 16: 4-[(3,5-dimethylphenyl)-thio]-3-iodo-6-methyl-5-morpholinomethyl-1*H*-pyridin-2-one (compound 43)



43

A mixture of compound 60 (0.05 g ; 0.1 mmol), morpholine (0.02 ml; 0.0002 mol) and K_2CO_3 (0.082g ; 0.6 mmol) in acetonitrile (2 ml; 0.6 mmol) was stirred at 50°C in a sealed tube for 2 hours, poured out into water and extracted with ethylacetate. The solvent was evaporated. The residue was crystallized from diisopropyl ether. The precipitate was filtered off and dried. The residue (0.057 g) was crystallized from isopropanol. The precipitate was filtered off and dried to yield 0.041 g (73 %), m.p. = 230°C.

Example 17: 6-(diethoxymethyl)-4-(3,5-dimethylphenoxy)-5-ethyl-3-iodo-2(1*H*)-pyridinone (compound 134)



134

17.1.: 6-(diethoxymethyl)-5-ethyl-4-hydroxy-2*H*-pyran-2-one (intermediate 19)

A solution of sodium hydride (60 % dispersion in mineral oil) in tetrahydrofurane (500 ml) was cooled at 0°C under nitrogen. 3-oxo-hexanoïc-acid ethyl ester (25 g ; 158 mmol) was added dropwise and the mixture was stirred at 0°C for 15 minutes. Butyllithium 1.6 M (99 ml; 158 mmol) was added dropwise and the mixture was stirred at 0°C for 1 hour. Diethoxy-acetic acid ethyl ester (27.8 g ; 0.178 mol) was added drop wise and the mixture was stirred at 0°C for 1 hour. Hydrochloric acid 12 N (50 ml) was added and the mixture was stirred at room temperature for 1 hour and extracted with diethyl ether to yield 20 g (53%) of intermediate 19. The product was used without further purification in the next reaction step.

17.2.: 6-(diethoxymethyl)-5-ethyl-4-hydroxy-2(1*H*)-pyridinone (intermediate 20)

A mixture of intermediate 19 (20 g ; 82 mmol) in CH_3OH/NH_3 (150 ml) was stirred at 60°C for 4 hours, evaporated till dryness and taken up in diisopropyl ether. The precipitate was filtered to yield 1.5 g of intermediate 20 (7.5 %). The product was used without further purification in the next reaction step.

17.3.: [6-(diethoxymethyl)-5-ethyl-4-hydroxy-2-oxo-3-pyridinyl]-(3,5-dimethylphenyl)-iodonium,hydroxide, inner salt (intermediate 21)

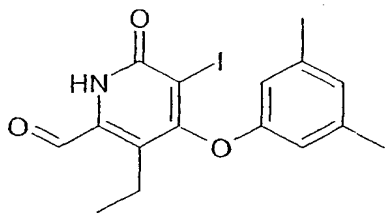
A mixture of intermediate 20 (3.4 g ; 14 mmol) and Na_2CO_3 (3 g ; 28 mmol) in water (50 ml) was stirred at room temperature for 15 min to give residue 1. A mixture of intermediate 2 (4.66 g ; 15.4 mmol) and Na_2CO_3 (3 g ; 28 mmol) in water (50 ml) was stirred at room temperature for 15 min to give residue 2. Residue 1 and residue 2 were combined and then stirred at room temperature for 2 hours. The

precipitate was filtered off, washed with water and dried. Yield 8 g of intermediate 21; m. p. = 125°C).

17.4.: 6-(diethoxymethyl)-4-(3,5-dimethylphenoxy)-5-ethyl-3-iodo-2(1*H*)-pyridinone (compound 134)

A mixture of intermediate 21 (6 g ; 12.7 mmol) in DMF (20 ml) was stirred at 120°C for 1 hour. The solvent was evaporated till dryness to yield 5 g of compound 134 (83 %). The residue was used immediately without further purification.

Example 18: 4-(3,5-dimethylphenoxy)-3-ethyl-1,6-dihydro-5-iodo-6-oxo–2-pyridinecarboxaldehyde (compound 159)

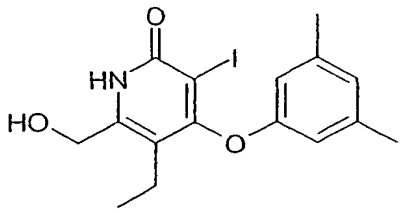


159

A mixture of compound 134 (5 g; 10 mmol) in HCl 3N (30 ml) and tetrahydrofurane (5 ml) was stirred at 100°C for 30 min. and then extracted with CH_2Cl_2. The organic layer was separated, dried, filtered and the solvent was evaporated. The residue (5g) was crystallized from diisopropyl ether. The precipitate was filtered off and dried to yield 3.5 g of titled compound 159 (83 %), m.p. = 158°C.

The residue was used without further purification.

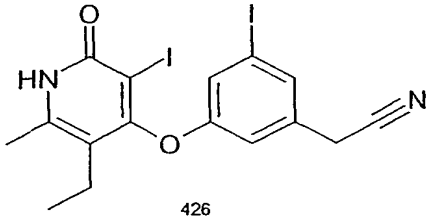
Example 19: 4-(3,5-dimethylphenoxy)-5-ethyl-6-(hydroxymethyl)-3-iodo-2(1*H*)-pyridinone (compound 133)



133

$NaBH_4$ (0.047 g ; 1.3 mmol) was added to a mixture of compound 159 (0.5g; 0.013 mol) in methanol (3 ml). The mixture was stirred at room temperature for 1 hour. Water was added. The precipitate was filtered off, taken up in diisopropyl ether and dried to yield 0.26 g (52 %), m. p. = 70°C).

Example 20: [3-(5-ethyl-3-iodo-6-methyl-2-oxo-1,2-dihydro-pyridin-4-yloxy)-5-iodo-phenyl]-acetonitrile (compound n° 426)

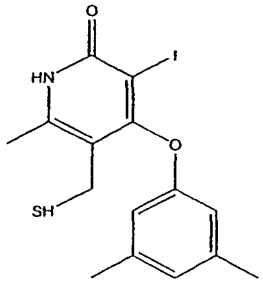


426

A mixture of compound 81 (0.1 g; 0.001 mol) and potassium cyanide (0.024 g; 0.0003 mol) in ethanol (2 ml) was stirred at 80°C in a celled tube overnight. H_2O was added. The mixture was extracted with CH_2Cl_2. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/1; 15-40 µm). The pure fractions were collected and the solvent was evaporated. The residue (0.03 g) was crystallized from DIPE. The precipitate was filtered off and dried to yield 0.21 g (21%), m.p. = 220°C.

Example 21: 4-(3,5-dimethylphenoxy)-3-iodo-6-methyl-5-[2-methylthiazol-4-ylmethylsulfanylmethyl)-1H-pyridin-2-one (compound n° 483)

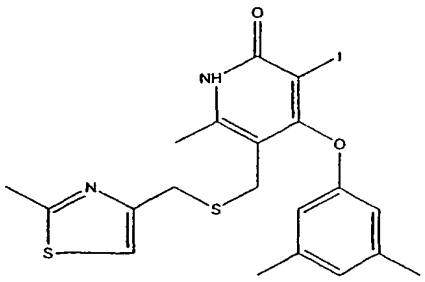
21.1: 4-(3,5-dimethylphenoxy)-3-iodo-5-mercaptomethyl-6-methyl-1H-pyridin-2-one (compound n° 451)



451

A mixture of compound 125 (1.5 g; 0.0037 mol) and thiourea (0.31 g; 0.00408 mol) in DMSO (30 ml) was stirred at room temperature for 1 hour. NaOH 3N was added. The mixture was stirred for 15 minutes, acidified with HCl 3N and extracted with ethylacetate (EtOAc). The organic layer was separated, dried on magnesium sulfate ($MgSO_4$), filtered and the solvent was evaporated. The residue was taken up in DIPE and filtered. The precipitate (1.2 g) was purified by column chromatography over silica gel (eluent: EtOAc 100%; 35-70 µm) and dried to yield 0.3 g (20%).

21.2: 4-(3,5-dimethylphenoxy)-3-iodo-6-methyl-5-[2-methylthiazol-4-ylmethyl-sulfanylmethyl)-1H-pyridin-2-one (compound n° 483)



483

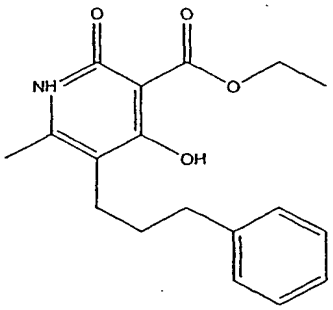
A mixture of compound 451 (0.07 g; 0.0001 mol) and 4-chloromethyl-2-methylthiazole (0.16 g; 0.0008 mol) in ethanol (3 ml) and triethylamine (0.2 ml) was stirred at 80°C for 1 hour. H_2O was added. The mixture was extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (0.04 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 98/2; 15-40 µm). The pure fractions were collected and the solvent was evaporated and dried to yield 0.018 g.

Example 22: 4-(3,5-dimethylphenoxy)-3-iodo-6-methyl-5-(3-phenyl-propyl)-1H-pyridin-2-one (compound 547)

22.1: 2-(1-amino-ethylidene)-5-phenyl-pentanoic acid ethyl ester (intermediate 23)

Ammonium nitrate (3.1 g; 0.039 mol) was added to a solution of intermediate 22 (2-acethyl-5-phenyl-pentanoic acid ethyl ester) (8.8 g; 0.0354 mol) in tetrahydrofuran (90 ml). Ammoniac was bubbled. The mixture was stirred and refluxed for 6 hours, then stirred at room temperature for 12 hours, poured out into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried on magnesium sulfate ($MgSO_4$), filtered and the solvent was evaporated and dried to yield 8.3 g.

22.2: ethyl 4-hydroxy-6-methyl-2-oxo-5-(3-phenyl-propyl)-1,2dihydro-pyridine-3-carboxylic acid ethyl ester (intermediate 24)

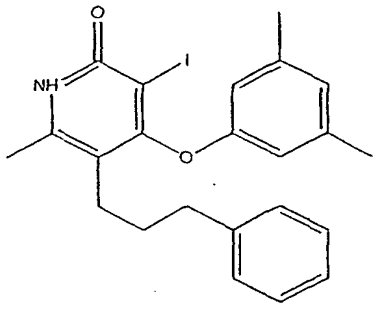


Sodium ethoxide in ethanol (27.5 ml; 0.0738 mol) was stirred and refluxed. Malonic acid diethyl ester (11.8 ml; 0.0738 mol) was added dropwise. A solution of intermediate 23 (8.3 g; 0.0335 mol) in ethanol (30 ml) was added dropwise. The mixture was stirred and refluxed for 15 hours. Three-quarters of EtOH were evaporated. The mixture was poured out in ice, acidified with HCl 3N and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (19.5 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/NH_4OH 96/4/0.1; 15-35 µm). Two fractions were collected and the solvent was evaporated and dried to yield 0.43 g (4%).

22.3: 4-hydroxy-6-methyl-5-(3-phenyl-propyl)-1H-pyridin-2-one (intermediate 25)

A mixture of intermediate 24 (0.1 g; 0.003 mol) and sodium hydroxide (0.038 g; 0.0009 mol) in H_2O (1.5 ml) was stirred and refluxed for 15 hours, then cooled to 5°C with HCl 3N. The precipitate was filtered, washed with H_2O, then with isopropanol and dried to yield 0.07 g (91%).

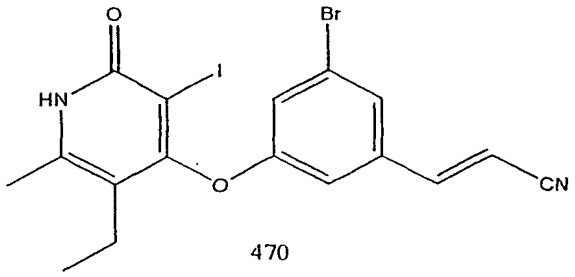
22.4: 4-(3,5-dimethylphenoxy)-3-iodo-6-methyl-5-(3-phenyl-propyl)-1H-pyridin-2-one (compound 547)



547

A mixture of dichloro-3,5-dimethyliodobenzene (0.096 g; 0.0003 mol) and sodium carbonate (0.12 g; 0.0005 mol) in dimethylformamide (1 ml; 0.5 ml) was stirred at room temperature for 30 minutes. A solution of intermediate 25 (0.07 g; 0.0002 mol) and sodium carbonate (0.6 g; 0.0005 mol) in H_2O (0.5 ml) was added. The mixture was stirred at room temperature for 1 hour. The precipitate was filtered, washed with H_2O, then with DIPE and dried. The residue (0.12 g) was taken up in DMF and stirred at 100°C for 30 minutes. The solvent was evaporated till dryness. The residue (0.1 g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 98/2/0 to 95/5/0.1; 35-70 µm). The pure fractions were collected and the solvent was evaporated. The residue (0.07 g) was taken up in iPrOH. The precipitate was filtered off and dried to yield 0.06 g (44%), m.p. = 220°C.

Example 23: 6-methyl-5-ethyl-3-iodo-4-[(3-bromo,5-acrylonitrilephenoxy]pyridin-2(1*H*)-one (compound 470)



470

23.1. 3-Bromo-5-iodobenzaldehyde dichloride (intermediate 26)

3-Bromo-5-iodobenzaldehyde dichloride (intermediate 26) was obtained as described by H.J. Lucas and E.R. Kennedy, Org. Synth. (1955), **III**, 482-483.

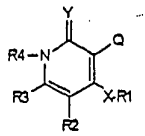
23.2. 6-methyl-5-ethyl-3-iodo-4-[(3-bromo,5-formylphenoxy]pyridin-2(1*H*)-one (compound 469)

Intermediate 26 (311 mg, 1 mmol) was suspended in 10 ml of water containing sodium carbonate (106 mg, 1 mmol) and stirred for 30 min. at room temperature. To this mixture a solution of 5-ethyl-6-methyl-4-hydroxypyridin-2(1*H*)-one (153 mg, 1 mmol) in 10 ml of water containing also Na_2CO_3 (106 mg, 1 mmol) was added. After stirring for 1h at 20°C the precipitate was filtered off, washed with water, dried *in vacuo* and suspended in dimethylformamide (5 mL). After heating at 120°C for 10 min., the solvent was removed. Purification by flash chromatography (SiO_2, CH_2Cl_2/EtOH 98:2) gave the titled compound (205 mg, 44%) as yellow microcrystals, m.p. >260°C.

23.3. 6-methyl-5-ethyl-3-iodo-4-[(3-bromo,5-acrylonitrilephenoxy]pyridin-2(1*H*)-one (compound 470)

To a 0°C magnetically stirred solution of diethyl(cyanomethyl)-phosphonate (113 µL, 0.68 mmol) in anhydrous THF (3 mL), NaH (28 mg; 0.68 mmol) was added (60% in mineral water). After stirring at room temperature for 1 h, compound 469 (80 mg; 0.17 mmol) was added and the reaction mixture was stirred 18 h at room temperature and poured into water (5 ml). The resulting solution was extracted with AcOEt, dried over $MgSO_4$ and evaporated. The oily residue obtained was then crystallized from Et_2O to give the pure titled compound (65 mg; 77%), m.p.> 260°C.

Table 1 lists intermediates and compounds of formula (I) which were made analogous to one of the above examples.

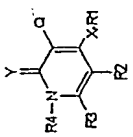


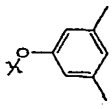
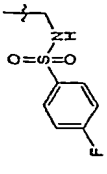
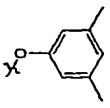
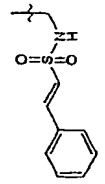
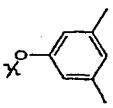
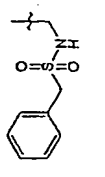
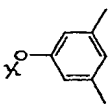
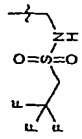
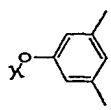
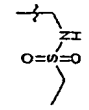
N°=	Y	Q	X-R1	R2	R3	R4	mp.°C / [MH+]
1	O	I	Chemistry 5	Chemistry 6	Me	H	245
2	O	I	Chemistry 11	Chemistry 12	Me	H	>250
3	O	I	Chemistry 17	Chemistry 18	Me	H	>250
4	O	I	Chemistry 23	Et	Chem 25	H	210

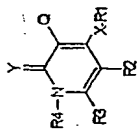
N°=	Y	Q	X-R1	R2	R3	R4	mp.°C / [MH+]
1	O	I	Chemistry 5	Chemistry 6	Me	H	245
2	O	I	Chemistry 11	Chemistry 12	Me	H	>250
3	O	I	Chemistry 17	Chemistry 18	Me	H	>250
4	O	I	Chemistry 23	Et	Chem 25	H	210

5	O	I	Chemistry 29	Chemistry 30	Me	H	>250
6	O	I	Chemistry 35	Chemistry 36	Me	H	[520]
7	O	i-Pr	Chemistry 41	Et	Me	H	260-262
8	O	I	Chemistry 47	Chemistry 48	Me	H	230
9	O	I	Chemistry 53	Et	Chem 55	H	125

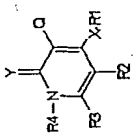
10	O	I	Chemistry 59	Chemistry 60	Me	H	[639]
11	O	I	Chemistry 65	Chemistry 66	Me	H	[569]
12	O	I	Chemistry 71	Chemistry 72	Me	H	[593]
13	O	I	Chemistry 77	Chemistry 78	Me	H	[539]
14	O	I	Chemistry 83	Chemistry 84	Me	H	[543]

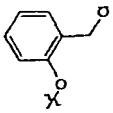
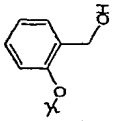
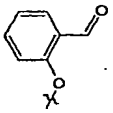
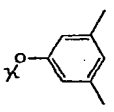
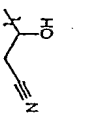
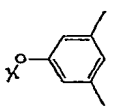
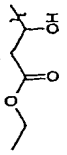


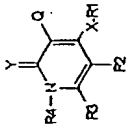
15	O	I	 Chemistry 89	 Chemistry 90	Me	H	[551]
16	O	I	 Chemistry 95	 Chemistry 96	Me	H	[539]
17	O	I	 Chemistry 101	 Chemistry 102	Me	H	[531]
18	O	I	 Chemistry 107	 Chemistry 108	Me	H	[477]
19	O	I	 Chemistry 113	 Chemistry 114	Me	H	[463]

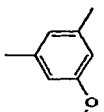
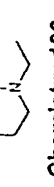
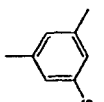
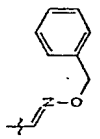
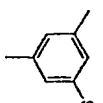
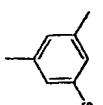
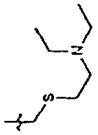
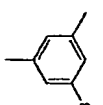
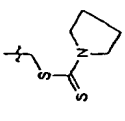


20	O	I	Chemistry 119	Chemistry 120	Me	H	[531]
21	O	Chem 124	Chemistry 125	I	Me	H	240-244
22	O	Chem 130	Chemistry 131	H	Me	H	192-194
23	O	I	Chemistry 137	Et	Me	H	102-104
24	O	I	Chemistry 143	Et	Me	H	170-172

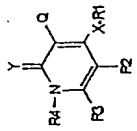


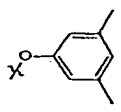
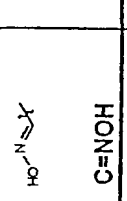
25	O	I	 Chemistry 149	Et	Me	H	225-226
26	O	I	 Chemistry 155	Et	Me	H	236-238
27	O	I	 Chemistry 161	Et	Me	H	260-262
28	O	I	 Chemistry 167	Et	 Chem 169	H	118
29	O	I	 Chemistry 173	Et	 Chem 175	H	184

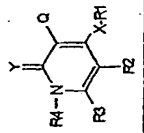


30	O	I	 Chemistry 179	 Chemistry 180	Me	H	160
31	O	I	 Chemistry 185	 Chemistry 186	Me	H	165
32	O	I	 Chemistry 191	 C=NOH	Me	H	>250
33	O	I	 Chemistry 197	 Chemistry 198	Me	H	150
34	O	I	 Chemistry 203	 Chemistry 204	Me	H	>250

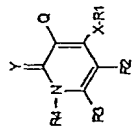
35	O	I	Chemistry 209	Chemistry 210	Me	H	>250
36	O	I	Chemistry 215	Chemistry 216	Me	H	200
37	O	I	Chemistry 221	Et	Chem223	H	[519]
38	O	I	Chemistry 227	Et	Chem 229	H	-----
39	O	I	Chemistry 233	Chemistry 234	Me	H	210

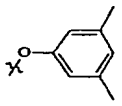
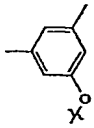
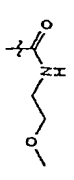
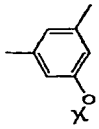
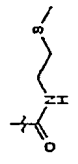
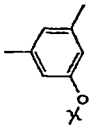
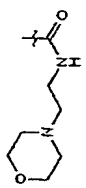
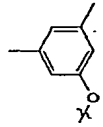
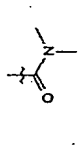


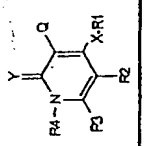
40	O	I	 Chemistry 239	Et	 Chem 241	H	210
41	O	I	Chemistry 245	Et	C=NOH	H	>250
42	O	I	Chemistry 251	Chemistry 252	Me	H	>250
43	O	I	Chemistry 257	Chemistry 258	Me	H	230
44	O	I	Chemistry 263	Chemistry 264	Me	H	120

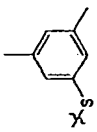
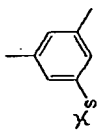
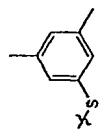
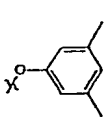
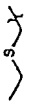
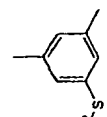


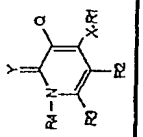
45	O	I	Chemistry 269	Chemistry 270	Me	H	210
46	O	I	Chemistry 275	Chemistry 276	Me	H	250
47	O	I	Chemistry 281	Chemistry 282	Me	H	>250
48	O	I	Chemistry 287	Et	Chem289	H	218
49	O	I	Chemistry 293	Chemistry 294	Me	H	>250

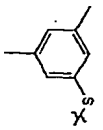
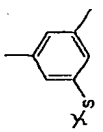
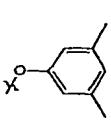
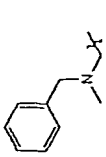
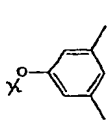
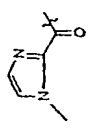
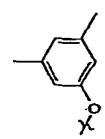
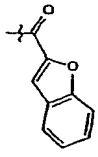


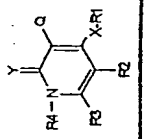
50	O	I	 Chemistry 299	Et	Chem 301	H	226
51	O	I	 Chemistry 305	 Chemistry 306	Me	H	236
52	O	I	 Chemistry 311	 Chemistry 312	Me	H	>250
53	O	I	 Chemistry 317	 Chemistry 318	Me	H	>250
54	O	I	 Chemistry 323	 Chemistry 324	Me	H	150

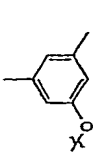
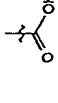
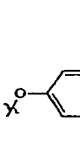
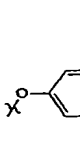
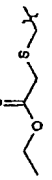
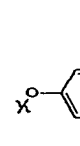
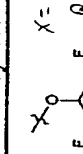


55	O	I	 Chemistry 329	 CN	Me	H	>250
56	O	H	 Chemistry 335	 CN	Me	H	>250
57	O	I	 Chemistry 341	 Formyl	Me	H	>250
58	O	I	 Chemistry 347	Et	 Chem 349	H	182
59	O	I	 Chemistry 353	 CH2NMe2	Me	H	245

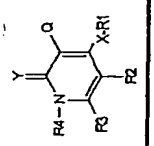


60	O	I	 Chemistry 359	 CH2Cl	Me	H	218
61	O	I	 Chemistry 365	CH2OH	Me	H	240
62	O	I	 Chemistry 371	Et	 Chem 373	H	165
63	O	I	 Chemistry 377	Et	 Chem 379	H	235
64	O	I	 Chemistry 383	 Chemistry 384	Me	H	>250

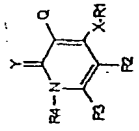


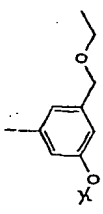
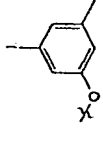
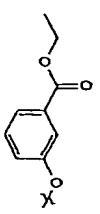
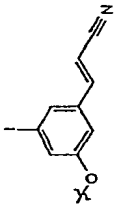
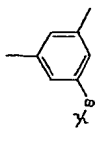
65	O	I	 Chemistry 389	 CO2H	Me	H	>250
66	O	I	 Chemistry 395	Et	 CH2CN	H	240
67	O	I	 Chemistry 401	Et	 Chem 403	H	[502]
68	O	Me	 Chemistry 407	Et	Me	H	207-209
69	O	H	 Chemistry 413	Et	Me	H	---

70	O	I	Chemistry 419	Et	Chem 421	H	224
71	O	I	Chemistry 425	CO2Et	Me	H	210
72	O	H	Chemistry 431	CO2Et	Me	H	230
73	O	I	Chemistry 437	Et	Chem 439	H	181
74	O	I	Chemistry 443	Et	Chem 445	H	170

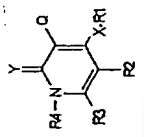


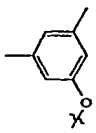
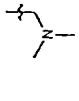
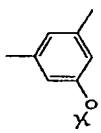
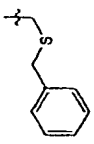
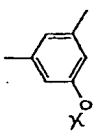
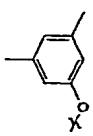
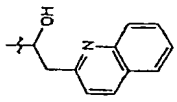
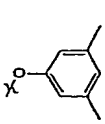
75	O	I	Chemistry 449	Et	Chem 451	H	95
76	O	I	Chemistry 455	Chemistry 456	Me	H	112
77	O	H	Chemistry 461	CO2Et	Azido	H	216-218
78	O	I	Chemistry 467	Ph	H	H	230-232
79	O	I	Chemistry 473	Et	Me	H	138-139

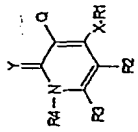


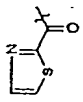
80	O	I	 Chemistry 479	Et	Me	H	178-179
81	O	I	 Chemistry 485	Et	Me	H	248-250
82	O	I	 Chemistry 491	Et	Me	H	202-204
83	O	I	 Chemistry 497	Et	Me	H	258-260
84	O	H	 Chemistry 503	 Chemistry 504	Me	H	205-207

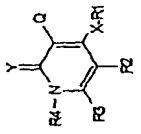
85	O	Br	Chemistry 509	Chemistry 510	Me	H	183-184
86	O	I	Chemistry 515	Chemistry 516	Me	H	220-222
87	O	CO2Et	Chemistry 521	Et	Me	H	189-191
88	O	I	Chemistry 527	Et	Me	H	----
89	O	H	Chemistry 533	Et	Me	H	229-231
90	O	I	Chemistry 539	Et	Me	H	288-290



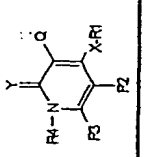
91	O	I	 Chemistry 545	 CH2NMe2	Me	H	238
92	O	I	 Chemistry 551	 Chemistry 552	Me	H	220
93	O	I	 Chemistry 557	Et	Chem 559	H	160
94	O	I	 Chemistry 563	 Chemistry 564	Me	H	218
95	O	I	 Chemistry 569	Et	Chem 571	H	214



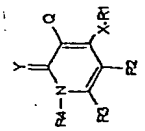
96	O	I	Chemistry 575	Et		H	190
97	O	I	Chemistry 581	Chemistry 582	Me	H	>250
98	O	I	Chemistry 587	Et		H	240
99	O	I	Chemistry 593	Chemistry 594	Me	H	180
100	O	I	Chemistry 599	Ac	Me	H	>250

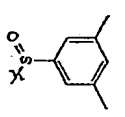


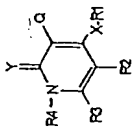
101	O	I	Chemistry 605	Et	(CH2)3	210
102	O	I	Chemistry 611	Et	Chem613	170
					H	
103	O	I	Chemistry 617	Et	Chem 619	170
					H	
104	O	I	Chemistry 623	Et	Chem 625	200
					H	
105	O	I	Chemistry 629	Et	Chemistry 631	>250
					H	

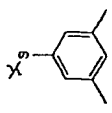
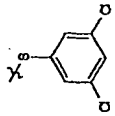
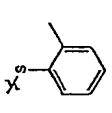
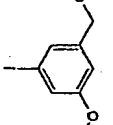
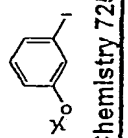


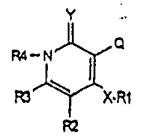
106	O	I	Chemistry 635	CO2Et	Azido	H	216-218
107	O	I	Chemistry 641	Et	Me	H	263-265
108	O	I	Chemistry 647	Et	Me	H	....
109	O	Br	Chemistry 653	Et	Me	H	187-189
110	O	I	Chemistry 659	Chemistry 660	Me	H	240

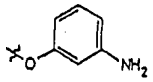
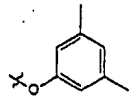
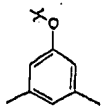
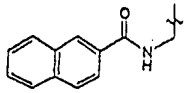
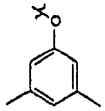
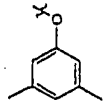


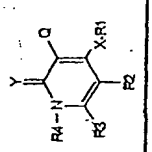
111	O	CO2Et	 Chemistry 665	Et	Me	H	202-204
112	O	H	Chemistry 671	CN	NH2	H	282-283
113	O	I	Chemistry 677	CN	NH2	H	283-285
114	O	H	3-Methylbenzyl	Et	Me	H	166-168
115	O	I	Chemistry 695	Et	Me	H	229-231

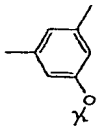
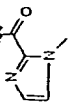
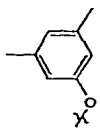
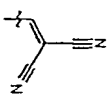
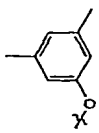
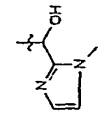
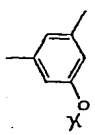
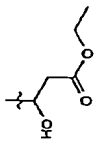
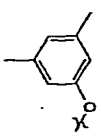


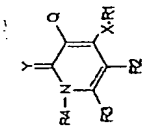
116	O	Br	 Chemistry 701	Et	CH2Br	H	[430]
117	O	H	 Chemistry 707	Et	Me	H	....
118	O	I	 Chemistry 713	Et	Me	H	....
119	O	I	 Chemistry 719	Et	Me	H	266-267
120	O	I	 Chemistry 725	Et	Me	H	186-187

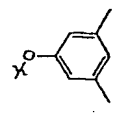
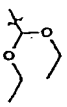
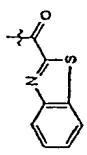


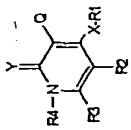
121	O	I	 Chemistry 731	Et	Me	H	225-226
122	O	I	 Chemistry 737	CN	 Azido	H	225-227
123	O	I	 Chemistry 743	 Chemistry 744	Me	H	[539]
124	O	I	 Chemistry 749	 Chemistry 750	Me	H	140
125	O	I	 Chemistry 755	CH2Cl	Me	H	256-258

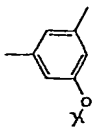
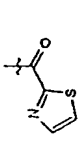
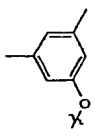
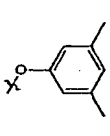
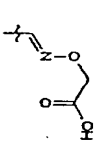
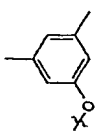
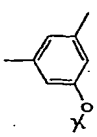
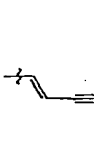


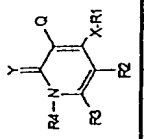
126	O	I	 Chemistry 761	 Chemistry 762	Me	H	>250
127	O	I	 Chemistry 767	 C=C(CN)2	Me	H	---
128	O	I	 Chemistry 773	 Chemistry 774	Me	H	>240
129	O	I	 Chemistry 779	 Chemistry 780	Me	H	230
130	O	I	 Chemistry 785	Et	 Chem787	H	180

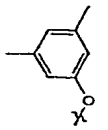
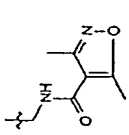
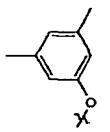
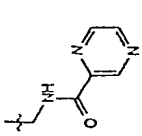
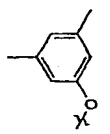
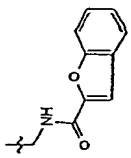
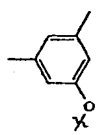
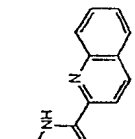


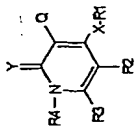
131	O	I	 Chemistry 791	Et	 CH2NMe2	H	130
132	O	I	Chemistry 797	Et	CH2Cl	H	>240
133	O	I	Chemistry 803	Et	CH2OH	H	97
134	O	I	Chemistry 809	Et	 Chem 811	H	----
135	O	I	Chemistry 815	 Chemistry 816	Me	H	>250



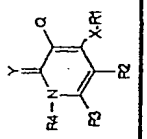
136	O	1	 Chemistry 821	 Chemistry 822	Me	H	>250
137	O	1	 Chemistry 827	Chemistry 828	Me	H	>250
138	O	1	 Chemistry 833	 Chemistry 834	Me	H	250
139	O	1	 Chemistry 839	Et	 Chem 841	H	[442]
140	O	1	 Chemistry 845	 CH=CHCN	Me	H	>250



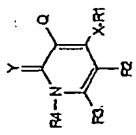
141	O	I	 Chemistry 851	 Chemistry 852	Me	H [508]
142	O	I	 Chemistry 857	 Chemistry 858	Me	H [491]
143	O	I	 Chemistry 863	 Chemistry 864	Me	H [529]
144	O	I	 Chemistry 869	 Chemistry 870	Me	H [540]

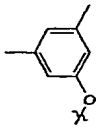
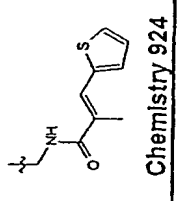
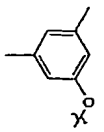
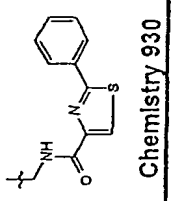
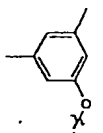
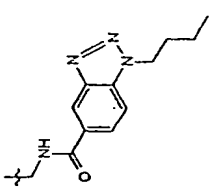
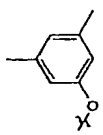
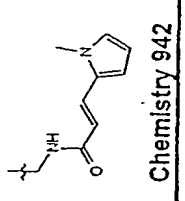


145	O	I	Chemistry 875	Chemistry 876	Me	H	[545]
146	O	I	Chemistry 881	Chemistry 882	Me	H	[543]
147	O	I	Chemistry 887	Chemistry 888	Me	H	[593]
148	O	I	Chemistry 893	Chemistry 894	Me	H	[544]

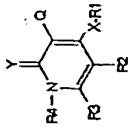


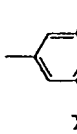
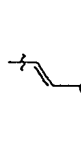
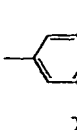
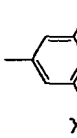
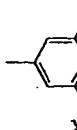
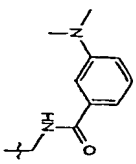
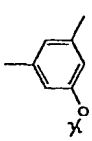
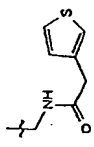
149	O	I	Chemistry 899	Chemistry 900	Me	H	[570]
150	O	I	Chemistry 905	Chemistry 906	Me	H	[516]
151	O	I	Chemistry 911	Chemistry 912	Me	H	[519]
152	O	I	Chemistry 917	Chemistry 918	Me	H	[569]

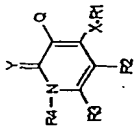


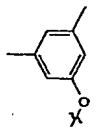
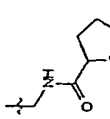
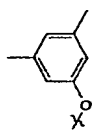
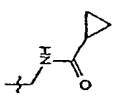
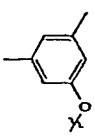
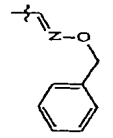
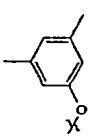
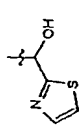
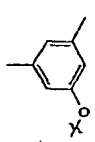
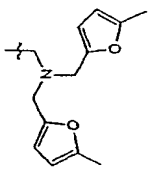
153	O	I	 Chemistry 923	 Chemistry 924	Me	H	[535]
154	O	I	 Chemistry 929	 Chemistry 930	Me	H	[572]
155	O	I	 Chemistry 935	 Chemistry 936	Me	H	[586]
156	O	I	 Chemistry 941	 Chemistry 942	Me	H	[518]

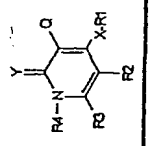
157	O	I	Chemistry 947	Et	Chem 949	H	195
158	O	I	Chemistry 963	Et	Chem 955	H	200
159	O	I	Chemistry 959	Et	Formyl	H	158
160	O	I	Chemistry 965	Chemistry 966	Me	H	>250
161	O	I	Chemistry 971	Chemistry 972	Me	H	196

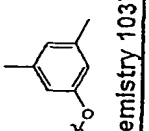
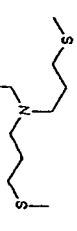
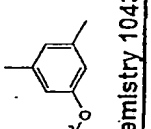
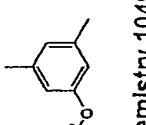
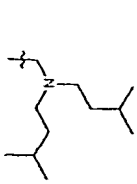
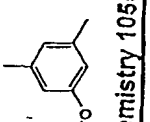
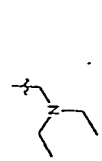
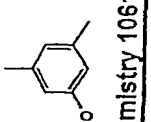


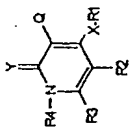
162	O	I	 Chemistry 977	 Chemistry 978	Me	H	220
163	O	I	 Chemistry 983	C=CHAc	Me	H	>240
164	O	I	 Chemistry 989	 Chemistry 990	Me	H	>240
165	O	I	 Chemistry 995	 Chemistry 996	Me	H	>240
166	O	I	 Chemistry 1001	 Chemistry 1002	Me	H	>250

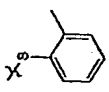


167	O	I	 Chemistry 1007	 Chemistry 1008	Me	H	242
168	O	I	 Chemistry 1013	 Chemistry 1014	Me	H	262
169	O	I	 Chemistry 1019	 Chemistry 1020	Me	H	>250
170	O	I	 Chemistry 1025	 Chemistry 1026	Me	H	230
171	O	I	 Chemistry 1031	 Chemistry 1032	Me	H	[573]

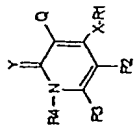


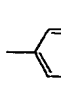
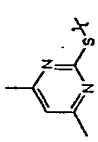
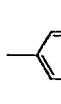
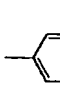
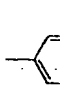
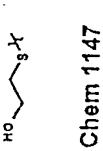
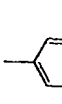
172	O	I	 Chemistry 1037	 Chemistry 1038	Me	H	[561]
173	O	I	 Chemistry 1043	 Chemistry 1044	Me	H	[593]
174	O	I	 Chemistry 1049	 Chemistry 1050	Me	H	[525]
175	O	I	 Chemistry 1055	 Chemistry 1056	Me	H	[441]
176	O	I	 Chemistry 1061	 C=NOH	Me	H	>250

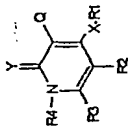


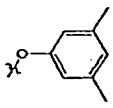
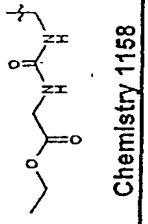
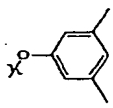
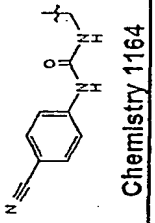
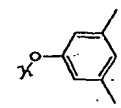
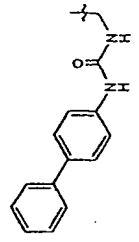
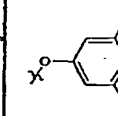
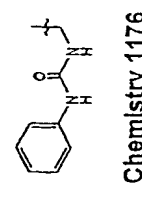
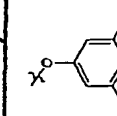
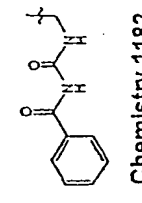
177	O	H	 Chemistry 1067	Et	Me	H	....
178	O	CO2Et	Chemistry 1073	Et	Me	H	....
179	O	CO2Et	Chemistry 1079	Et	Me	H	....
180	O	n-Pr	Chemistry 1085	Et	Me	H	158-160
181	O	I	Chemistry 1091	Me	H	H	>260

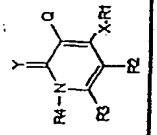
182	O	Chem1096	Chemistry 1097	Et	Me	H	158-160
183	O	Chem 1102	Chemistry 1103	Et	Me	H	159-161
184	O	I	Chemistry 1109	CN	Chem 1111	H	261-262
185	O	I	Chemistry 1115	CN	Chem 1117	H	263-264
186	O	I	Chemistry 1121	CN	SPh	H	265-267



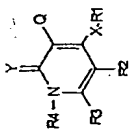
187	O	I	 Chemistry 1127	CN	 Chem 1129	H	224-225
188	O	I	 Chemistry 1133	CN	 Chem1135	H	218-220
189	O	I	 Chemistry 1139	CN	 Chem 1141	H	235-237
190	O	I	 Chemistry 1145	CN	 Chem 1147	H	242-244
191	O	I	 Chemistry 1151	Et	CH2CH2Ph	H	240



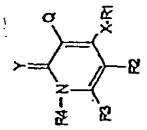
192	O	I	 Chemistry 1157	 Chemistry 1158	Me	H [514]
193	O	I	 Chemistry 1163	 Chemistry 1164	Me	H [529]
194	O	I	 Chemistry 1169	 Chemistry 1170	Me	H [580]
195	O	I	 Chemistry 1175	 Chemistry 1176	Me	H [504]
196	O	I	 Chemistry 1181	 Chemistry 1182	Me	H [562]

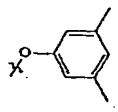
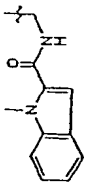
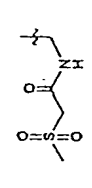
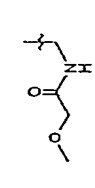
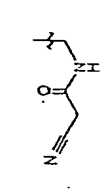
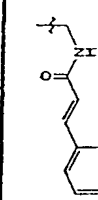


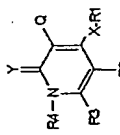
197	O	I	Chemistry 1187	Chemistry 1188	Me	H	[518]
198	O	I	Chemistry 1193	Chemistry 1194	Me	H	[456]
199	O	I	Chemistry 1199	Chemistry 1200	Me	H	[503]
200	O	I	Chemistry 1205	Chemistry 1206	Me	H	[545]
201	O	I	Chemistry 1211	Chemistry 1212	Me	H	[469]

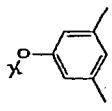
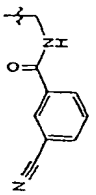
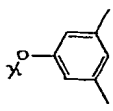
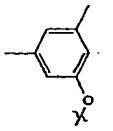
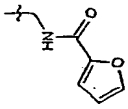
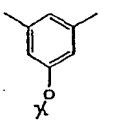
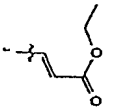
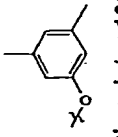


202	O	I	Chemistry 1217	Chemistry 1218	Me	H	[513]
203	O	I	Chemistry 1223	Chemistry 1224	Me	H	[538]
204	O	I	Chemistry 1229	Chemistry 1230	Me	H	[481]
205	O	I	Chemistry 1235	Chemistry 1236	Me	H	[490]
206	O	I	Chemistry 1241	Chemistry 1242	Me	H	[492]

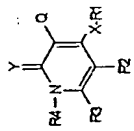


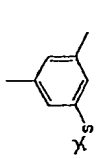
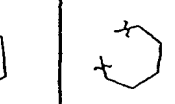
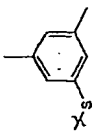
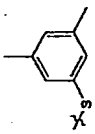
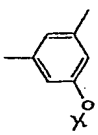
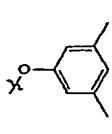
207	O	I	 Chemistry 1247	 Chemistry 1248	Me	H [542]
208	O	I	Chemistry 1253	 Chemistry 1254	Me	H [506]
209	O	I	Chemistry 1259	 Chemistry 1260	Me	H [457]
210	O	I	Chemistry 1265	 Chemistry 1266	Me	H [452]
211	O	I	Chemistry 1271	 Chemistry 1272	Me	H [516]

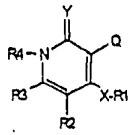


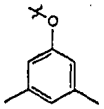
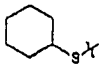
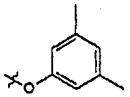
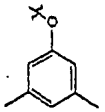
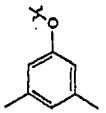
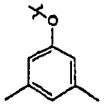
212	O	I	 Chemistry 1277	 Chemistry 1278	Me	H	[514]
213	O	I	 Chemistry 1283	 Chemistry 1284	Me	H	[427]
214	O	I	 Chemistry 1289	 Chemistry 1290	Me	H	>250
215	O	I	 Chemistry 1295	 CH=CHCO2Et	Me	H	>250
216	O	I	 Chemistry 1301	Et	 Chem 1303	H	160

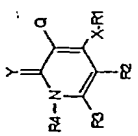
217	O	I	Chemistry 1307	Et	Chem 1309	H	230
218	O	I	Chemistry 1313	Chemistry 1314	Me	H	>250
219	O	I	Chemistry 1319	Chemistry 1320	Me	H	>250
220	O	I	Chemistry 1325	CH2NH2	Me	H	240
221	O	I	Chemistry 1331	Chemistry 1332		H	264-265



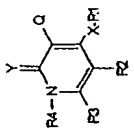
222	O	I	 Chemistry 1337	 (CH2)4	H	252-253
223	O	I	 Chemistry 1343	 (CH2)3	H	243-244
224	O	H	 Chemistry 1349	Chemistry 1350	H	260-262
225	O	I	 Chemistry 1355	CO2Et	Me	190
226	O	I	 Chemistry 1361	Et	Cl	146-147
						NH2

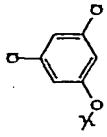
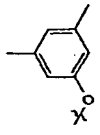
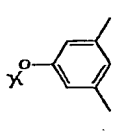
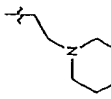
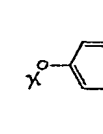
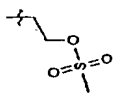
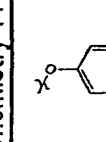


227	O	I	 Chemistry 1367	CN	 Chem 1369	H	282-284
228	O	I	 Chemistry 1373	CO2Et	Cl	H	180-182
229	O	H	 Chemistry 1379	CN	Cl	H	240-242
230	O	 Chem 1384	 Chemistry 1385	Et	Me	H	188-190
231	O	Et	 Chemistry 1391	Et	Me	H	179-181

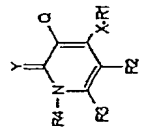


232	O	I	Chemistry 1397	Chemistry 1398	Me	H	>240
233	O	I	Chemistry 1403	Chemistry 1404	Me	H	[539]
234	O	Vinyl	Chemistry 1409	Et	Me	H	198-200
235	O	H	Chemistry 1415	(CH2)3		H	---
236	O	I	Chemistry 1421	CN	Cl	H	276-277

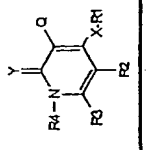


237	O	I	 Chemistry 1427	Et	Me	H	280-282
238	O	I	 Chemistry 1433	CN	Me	H	>240
239	O	I	 Chemistry 1439	 Chemistry 1440	Me	H	>240
240	O	I	 Chemistry 1445	 Chemistry 1446	Me	H	....
241	O	I	 Chemistry 1451	 Chemistry 1452	Me	H	>240

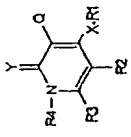
242	O	I	Chemistry 1457	Chemistry 1458	Me	H	220
243	O	I	Chemistry 1463	Chemistry 1464	Me	H	216-217
244	O	I	Chemistry 1469	Chemistry 1470	Me	H	216-218
245	O	I	Chemistry 1475	Chemistry 1476	Me	H	212-214
246	O	Chem 1480	3-Methylbenzyl	Et	Me	H	....



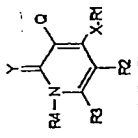
247	S	H	Chemistry 1487	Et	Me	H	>240
248	S	I	Chemistry 1493	Et	Me	H	210
249	O	I	Chemistry 1505	2-Methoxyethyl	Me	H	156
250	O	I	Chemistry 1511	Chemistry 1512	Me	H	141
251	O	Chem 1516	3-Methylbenzyl	Et	Me	H	----

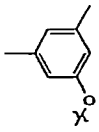
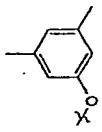
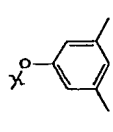
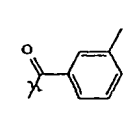
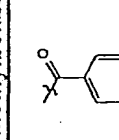


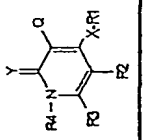
252	O	Chem 1522	3-Methylbenzyl	Et	Me	H	....
253	O	I	Chemistry 1529	Chemistry 1530	Me	H	184-186
254	O	I	Chemistry 1535	Chemistry 1536	Me	H	224-226
255	O	I	Chemistry 1541	Chemistry 1542	Me	H	234-236
256	O	I	Chemistry 1547	Chemistry 1548	H	H	160-162



257	O	I	Chemistry 1553	CH2OH	Me	H	248-250
258	O	I	Chemistry 1559	Et	Me	Me	240
259	O	I	Chemistry 1565	Et	Me	Chem 1562	179
260	O	SOMe	Chemistry 1571	Et	Me	H	196-197
261	O	I	Chemistry 1577	Et	Cl	H	186-187



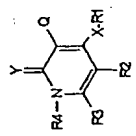
262	O	H	 Chemistry 1583	Me	Cl	H	210-242
263	O	I	 Chemistry 1589	Me	Cl	H	240-242
264	O	I	 Chemistry 1595	2-Methoxyethyl	Me	H	212
265	O	H	 3-Methylbenzoyl	Me	 Chem 1603	H	176
266	O	I	 3-Methylbenzoyl	Me	 Chem 1609	H	>260

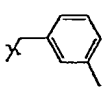


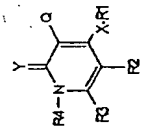
267	O	H	Chemistry 1613	Et	Cl	H	210-211
268	O	CH2OH	Chemistry 1619	H	Me	H	212-214
269	O	I	Chemistry 1625	Formyl	Me	H	282-284
270	O	Chem 1630	Chemistry 1631	Et	Me	H	192
271	O	Chem 1636	Chemistry 1637	Et	Me	H	182

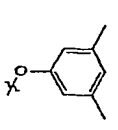
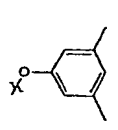
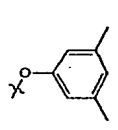
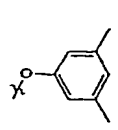
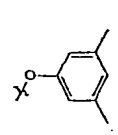
272	O	SMe	Chemistry 1643	Et	Me	H	186-188
273	O	Chem 1648	3-Methylbenzyl	Et	Me	H	[336]
274	S	Chem 1654	3-Methylbenzyl	Et	Me	H	[313]
275	O	CO2Me	3-Methylbenzyl	Et	Me	H	[300]
276	O	C=NOH	Chemistry 1667	Et	Me	H	262

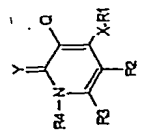
277	O	OMe	Chemistry 1673	Et	Me	H	178
278	O	Chem 1678	Chemistry 1679	Et	Me	H	225
279	O	Chem 1684	Chemistry 1685	Et	Me	H	166
280	O	SPh	Chemistry 1691	Et	Me	H	211
281	O	CH(OH)Ph	Chemistry 1697	Et	Me	H	198

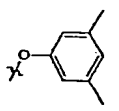
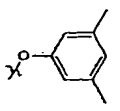
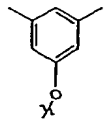
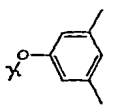
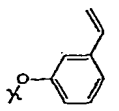


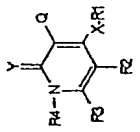
282	O	CO2Et	 3-Methylbenzyl	Et	Me	H	....
283	O	CO2H	3-Methylbenzyl	Et	Me	H	....
284	O	Br	Chemistry 1715	Et	Me	H	240-241
285	O	CN	Chemistry 1721	Et	Me	H	282-284
286	O	I	3-Methylbenzyl	Et	Me	H	204-206



287	O	I	 Chemistry 1733	H	Me	H	274-275
288	O	CCPh	 Chemistry 1739	Et	Me	H	260
289	O	CH=CHCO2Et	 Chemistry 1745	Et	Me	H	256
290	O	Formyl	 Chemistry 1751	Et	Me	H	228
291	O	3-Thlophenyl	 Chemistry 1757	Et	Me	H	222

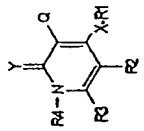


292	O	3-Cl-phenyl	 Chemistry 1763	Et	Me	H	223
293	O	2-Furyl	 Chemistry 1769	Et	Me	H	228
294	O	CH2OH	 Chemistry 1775	Et	Me	H	200
295	O	CO2H	 Chemistry 1781	Et	Me	H	221
296	O	I	 Chemistry 1787	Et	Me	H	232-234

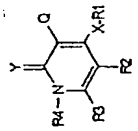


297	O	I	Chemistry 1793	Et	Me	H	248-250
298	O	I	Chemistry 1799	Et	Me	H	250
299	O	I	Chemistry 1806	Et	Me	H	265-266
300	O	I	Chemistry 1811	Et	Me	H	275-276

301	O	CO2H	2,5-Dimethoxybenzyl	H	H	H	[290]
302	O	H	Chemistry 1823	H	Me	H	[283]
303	O	CO2Et	Chemistry 1829	H	Me	H	[355]
304	O	CO2H	Chemistry 1835	H	Me	H	[299]
305	O	CO2Et	Chemistry 1841	H	Me	H	[303]

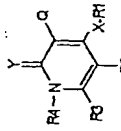


306	O	I	Chemistry 1859	Et	Me	H	200-202
307	O	I	Chemistry 1865	Et	Me	H	238-240
308	O	H	3,5-Dimethylbenzyl	Et	Me	H	212-214
309	O	I	Chemistry 1877	Et	Me	H	258-260
310	O	I	Chemistry 1883	Et	Me	H	---
311	O	I	Chemistry 1889	Et	Me	H	198-199

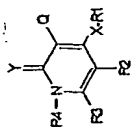


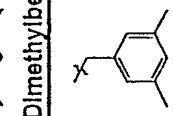
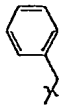
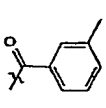
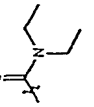
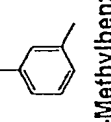
312	O	I	Chemistry 1895	Et	Me	H	182-183
313	O	I	Chemistry 1901	Et	Me	H	265-266
314	O	I	Chemistry 1907	Et	H	H	210-212
315	O	I	Chemistry 1913	Me	Me	H	261-262
316	O	I	Chemistry 1919	Chemistry 1920		H	218-219

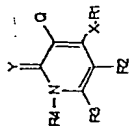
317	O	I	Chemistry 1925	(CH2)4	Et	H	230-232
318	O	I	Chemistry 1931	(CH2)3	Et	H	206-208
319	O	I	Chemistry 1937		Me	H	242-243
320	O	H	Chemistry 1943		Me	H	241-242
321	O	I	Chemistry 1949		Me	H	198-200
322	O	I	Chemistry 1955		Me	H	....



323	O	CO2Et	Chemistry 1961	Et	Me	H	198
324	O	CO2Et	3,5-Dimethylbenzyl	Et	Me	H	184-185
325	O	H	Chemistry 1973	Et	Me	H	232-233
326	O	I	Chemistry 1979	Et	Me	H	240
327	O	H	OPh	Et	Me	H	228-229
328	O	I	OPh	Et	Me	H	180-182
329	O	I	OPh	H	Me	H	265-266
330	O	CO2Et	Chemistry 2003	Et	Me	H	228-229

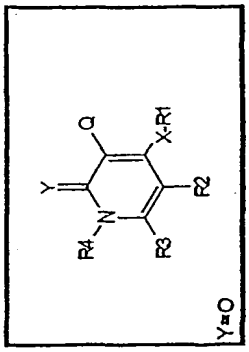


331	O	 Chem 2008	 3,5-Dimethylbenzyl	Et	Me	H	192-193
332	O	CO2H	3,5-Dimethylbenzyl	Et	Me	H	----
333	O	CN	 Benzyl	H	n-Pr	H	132
334	O	 Chem 2026	 3-Methylbenzoyl	Et	Me	H	207
335	O	 Chem 2032	 3-Methylbenzyl	Et	Me	H	216



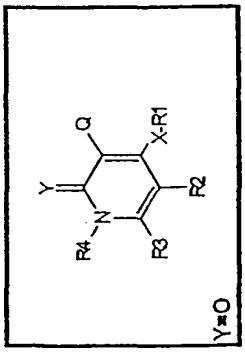
336	O	CH_2NMe_2	3-Methylbenzyl	$(CH_2)_4$	H
337	O	CH_2NH_2	3-Methylbenzyl	$(CH_2)_4$	H
....					185

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
338	I	Chemistry 3	Chemistry 4	Me	H	245
339	I	Chemistry 8	Chemistry 9	Me	H	175
340	I	Chemistry 13	Chemistry 14	Me	H	[460]
341	H	Chemistry 18	Et	Me	H	[324,326]
342	Cl	Chemistry 23	Et	Me	H	[292,294]

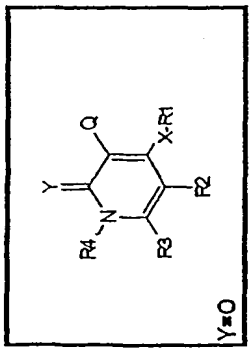


N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
343	Chemistry 27	Chemistry 28	Et	Me	H	[298]
344	I	Chemistry 33	Et	Me	H	[462]
345	I	Chemistry 38	Et	Me	H	[588]
346	I	Chemistry 43	Chemistry 44	Me	H	[506
347	CH2OH	Chemistry 48	Et	Me	H	[304]

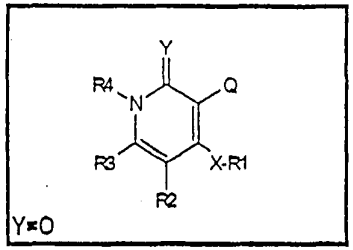
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
348	I	Chemistry 53	Et	Me	H	[627]
349	I	Chemistry 58	Et	Me	H	[610]
350	I	Chemistry 63	Et	Me	H	[618]
351	I	Chemistry 68	Et	Me	H	[604]
352	I	Chemistry 73	Et	Me	H	[615]

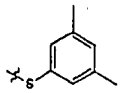
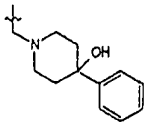
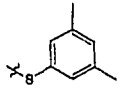
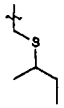
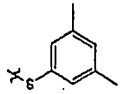
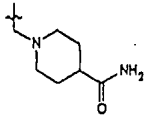
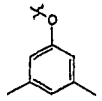
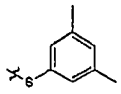
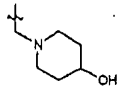


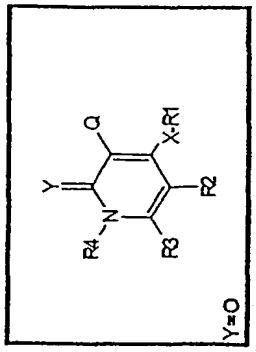
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
353	I	Chemistry 78	Et	Me	H	[579
354	I	Chemistry 83	Et	Me	H	[596]
355	I	Chemistry 88	Et	Me	H	[640]
356	I	Chemistry 93	Et	Me	H	[614]
357	I	Chemistry 98	Chemistry 99	Me	H	205

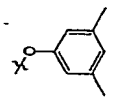
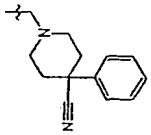
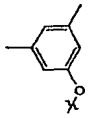
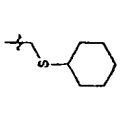
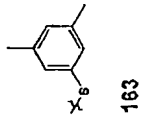
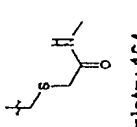
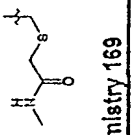


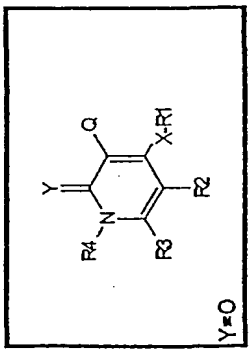
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
358	I	Chemistry 103	Chemistry 104	Me	H	210
359	I	Chemistry 108	Chemistry 109	Me	H	>250
360	I	Chemistry 113	Chemistry 114	Me	H	[487]
361	I	Chemistry 118	Chemistry 119	Me	H	[570]
362	I	Chemistry 123	Chemistry 124	Me	H	[455]



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
363	I	 Chemistry 128	 Chemistry 129	 Me	H	215
364	I	 Chemistry 133	 Chemistry 134	 Me	H	205
365	I	 Chemistry 138	 Chemistry 139	 Me	H	>250
366	I	 Chemistry 143	 Chemistry 144	Me	H	240
367	 I	 Chemistry 148	 Chemistry 149	Me	H	135

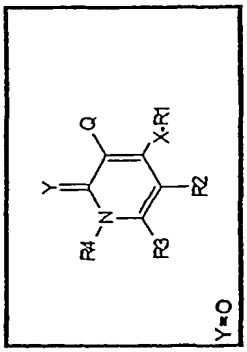


N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
368		 Chemistry 153	 Chemistry 154	Me	H	>250
369		 Chemistry 158	 Chemistry 159	Me	H	>250
370		 Chemistry 163	 Chemistry 164	Me	H	>250
371		Chemistry 168	 Chemistry 169	Me	H	>250
372		Chemistry 173	Chemistry 174	Me	H	>250

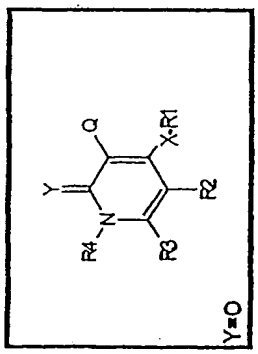


N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
373	I	Chemistry 178	Chemistry 179	Me	H	>250
374	I	Chemistry 183	Chemistry 184	Me	H	170
375	I	Chemistry 188	Chemistry 189	Me	H	220
376	I	Chemistry 193	Chemistry 194	Me	H	>250
377	I	Chemistry 198	Et	Chemistry 200	H	>250

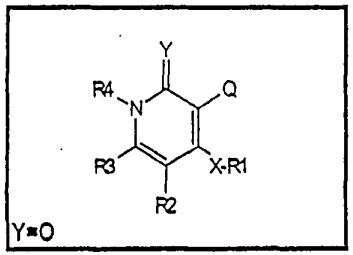
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
378	I	Chemistry 203	Chemistry 204	Me	H	>250
379	I	Chemistry 208	Et	CN	H	[395]
380	I	Chemistry 213	Et	CH2NH2	H	[398]
381	I	Chemistry 218	Chemistry 219	Me	H	230
382	I	Chemistry 223	Chemistry 224	Me	H	226



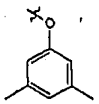
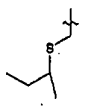
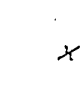
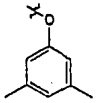
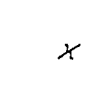
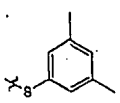
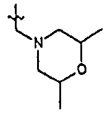
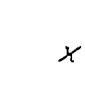
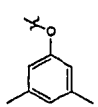
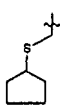
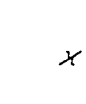
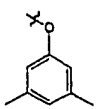
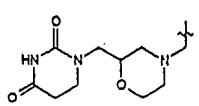
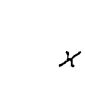
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
383	Chemistry 227	Chemistry 228	Et	Me	H	[532]
384	I	Chemistry 233	Chemistry 234	Me	H	[540]
385	I	Chemistry 238	Chemistry 239	Me	H	[512]
386	Vinyl	Chemistry 243	H	Me	H	[266]
387	Et	Chemistry 248	H	Me	H	[268]
388	Et	Chemistry 253	I	Me	H	[384]



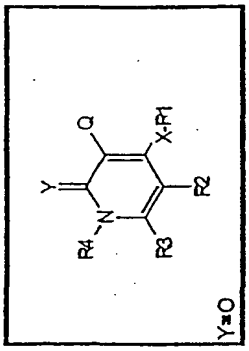
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
389	I	Chemistry 258	Chemistry 259	Me	H	>250
390	I	Chemistry 263	Chemistry 264	Me	H	>250
391	I	Chemistry 268	CH2NH2	Me	H	>260
392	I	Chemistry 273	Chemistry 274	Me	H	239
393	I	Chemistry 278	Chemistry 279	Me	H	220



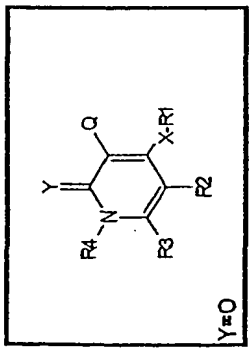
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
394	 I	Chemistry 283	 Chemistry 284	 Me	H	[458]
395	 I	Chemistry 288	 Chemistry 289	 Me	H	240
396	 I	Chemistry 293	 Chemistry 294	 Me	H	190
397	 I	Chemistry 298	 Chemistry 299	 Me	H	>240
398	 I	Chemistry 303	 Chemistry 304	 Me	H	>250

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
399	1	Chemistry 308	Chemistry 309	Me	H	>250
400	1	Chemistry 313	Chemistry 314	Me	H	>250
401	1	Chemistry 318	Chemistry 319	Me	H	212
402	1	Chemistry 323	Chemistry 324	Me	H	238
403	1	Chemistry 328	Chemistry 329	Me	H	188



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
404	I	Chemistry 333	Chemistry 334	Me	H	104
405	I	Chemistry 338	Chemistry 339	Me	H	240
406	I	Chemistry 343	Chemistry 344	Me	H	148
407	I	Chemistry 348	Et	Chemistry 350	H	214
408	Cl	Chemistry 353	Et	Me	H	[308,310]



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
409	CF3	Chemistry 368	Et	Me	H	[326]
410	I	Chemistry 363	Chemistry 364	Me	H	[541]
411	I	Chemistry 368	Chemistry 369	Me	H	[429]
412	I	Chemistry 373	Chemistry 374	Me	H	220
413	I	Chemistry 378	Chemistry 379	Me	H	>250

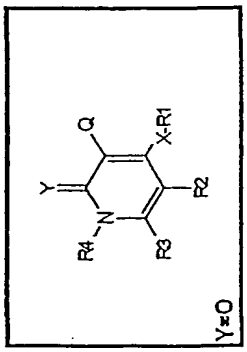
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
414	I	Chemistry 383	Chemistry 384	Me	H	[557]
415	I	Chemistry 388	Chemistry 389	Me	H	162
416	I	Chemistry 393	Chemistry 384	Me	H	>240
417	Chemistry 397	Chemistry 398	Et	Me	H	[328]
418	Chemistry 402	Chemistry 403	Et	Me	H	[362,364]

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
419	I	Chemistry 408	Chemistry 409	Me	H	248
420	I	Chemistry 413	Chemistry 414	Me	H	226
421	I	Chemistry 418	Chemistry 419	Me	H	174
422	H	Chemistry 423	Et	CH(OH)Ph	H	[350]
423	I	Chemistry 428	Et	CH(OH)Ph	H	[476]

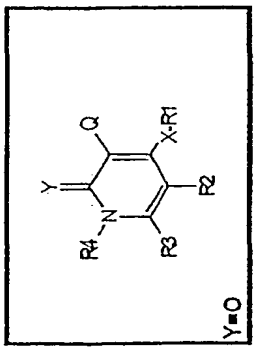
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
424						
	I	Chemistry 433	Chemistry 434	Me	H	156
425						
	I	Chemistry 438	Chemistry 439	Me	H	236
426						
	I	Chemistry 443	Et	Me	H	[521]
427						
	I	Chemistry 448	Chemistry 449	Me	H	234
428						
	I	Chemistry 453	Chemistry 454	Me	H	204
429						
	I	Chemistry 458	CO2Et	Me	H	[556]

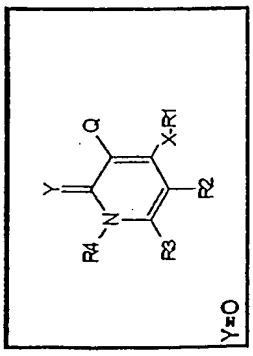
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
430	I	Chemistry 463	Et	Me	H	[574]
431	Chemistry 467	Chemistry 468	Et	Me	H	[410]
432	Chemistry 472	Chemistry 473	Et	Me	H	[432]
433	I	Chemistry 478	Chemistry 479	Me	H	236
434	I	Chemistry 483	Chemistry 484	Me	H	>250

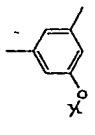
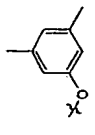
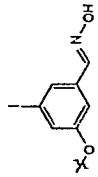
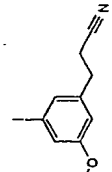


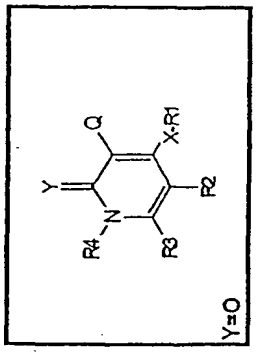
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
435	I	Chemistry 488	Chemistry 489	Me	H	200
436	I	Chemistry 493	Chemistry 494	Me	H	>250
437	I	Chemistry 498	Et	Chemistry 500	H	[442]
438	I	Chemistry 503	Et	Chemistry 505	H	186
439	I	Chemistry 508	Me	Me	H	[370]



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
440	I	Chemistry 513	CH2OH	Me	H	[514]
441	I	Chemistry 518	Me	Me	H	[372]
442	I	Chemistry 523	Me	Me	H	[390,392]
443	I	Chemistry 528	Me	Me	H	[380]
444	I	Chemistry 533	Me	Me	H	[430]



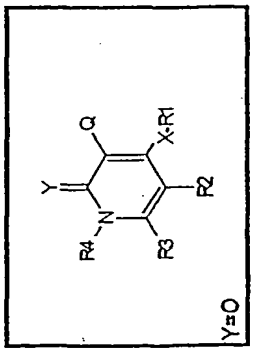
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
445	Chemistry 537	 Chemistry 538	 Et	 Me	H	[314]
446	Chemistry 542	 Chemistry 543	Et	Me	H	[356]
447	I	 Chemistry 548	Et	Me	H	[525]
448	I	 Chemistry 553	Et	Me	H	[535]
449	I	Chemistry 558	 Chemistry 559	Me	H	>240



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
450		Chemistry 563	Chemistry 564	Me	H	230
451		Chemistry 568	Chemistry 569	Me	H	230
452		Chemistry 573	Chemistry 574	Me	H	140
453		Chemistry 578	CO2Me	CH2OMe	H	210
454		Chemistry 583	CH2OH	CH2OMe	H	230
455		Chemistry 588	CH2Cl	CH2OMe	H	[434,436]

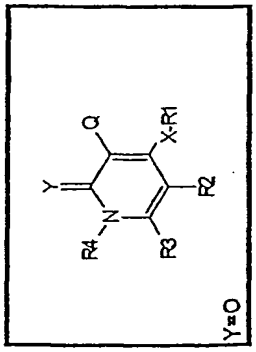
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
456	I	Chemistry 593	Chemistry 594	CH2OMe	H	232
457	I	Chemistry 598	Chemistry 599	CH2OH	H	230
458	I	Chemistry 603	Chemistry 604	Me	H	188
459	I	Chemistry 608	Chemistry 609	Me	H	190
460	I	Chemistry 613	Chemistry 614	Me	H	240

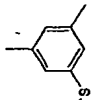
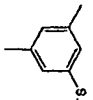
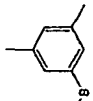
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
461		Chemistry 618	Chemistry 619	Me	H	204
462		Chemistry 623	Chemistry 624	Me	H	248
463		Chemistry 628	Chemistry 629	Me	H	220
464		Chemistry 633	Chemistry 634	Me	H	[583]
465		Chemistry 638	Chemistry 639	Me	H	[576,578]



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
466	I	Chemistry 643	Chemistry 644	Me	H	[560,562]
467	I	Chemistry 648	Chemistry 649	Me	H	[542]
468	I	Chemistry 653	Chemistry 654	Me	H	[558]
469	I	Chemistry 658	Et	Me	H	[462,464]
470	I	Chemistry 663	Et	Me	H	[485,487]

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
471	Chemistry 667	Chemistry 668	Et	Me	H	[390]
472	I	Chemistry 673	Et	Me	H	[506]
473	I	Chemistry 678	Et	Me	H	[507]
474	H	Chemistry 683	CO2Me	CH2OMe	H	165
475	H	Chemistry 688	CH2OH	CH2OMe	H	[306]
476	I	Chemistry 693	CO2Me	CH2OMe	H	142



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
477		 Chemistry 698	 CH2OH	 CH2OMe	H	198
478		 Chemistry 703	CH2Cl	CH2OMe	H	
479		 Chemistry 708	Chemistry 709	CH2OMe	H	116
480		 Chemistry 713	Chemistry 714	CH2OH	H	[487]
481		 Chemistry 718	Chemistry 719	Me	H	230

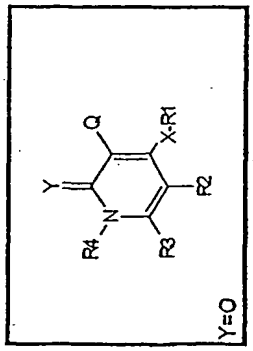
Y=O

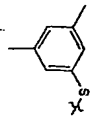
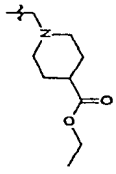
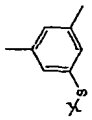
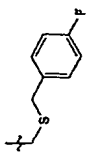
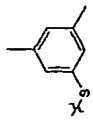
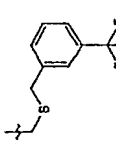
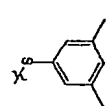
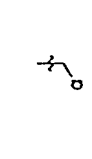
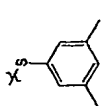
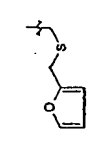
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
482	I	Chemistry 723	Chemistry 724	Me	H	168
483	I	Chemistry 728	Chemistry 729	Me	H	[513]
484	I	Chemistry 733	Chemistry 734	Me	H	200
485	I	Chemistry 738	Chemistry 739	Me	H	[486]
486	I	Chemistry 743	Chemistry 744	Me	H	220

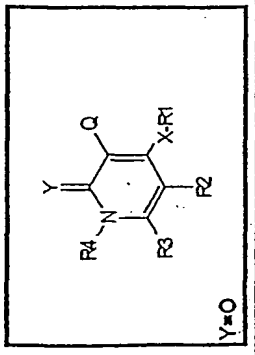
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
487	I	Chemistry 748	Chemistry 749	Me	H	174
488	I	Chemistry 753	Chemistry 754	Me	H	204
489	I	Chemistry 758	Chemistry 759	Me	H	>250
490	I	Chemistry 763	Chemistry 764	Me	H	162
491	I	Chemistry 768	Chemistry 769	Me	H	[600]

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
492	I	Chemistry 773	Chemistry 774	Me	H	[500]
493	I	Chemistry 778	Chemistry 779	Me	H	164
494	I	Chemistry 783	Chemistry 784	Me	H	[513]
495	I	Chemistry 788	Chemistry 789	Me	H	206
496	I	Chemistry 793	Chemistry 794	Me	H	185

N°=	Q	X-R1	R2	R3	R4	mp.°C./ (MH+)
497	I	Chemistry 788	Chemistry 799	CH2OMe	H	[460]
498	I	Chemistry 803	Chemistry 804	Me	H	[498]
499	I	Chemistry 808	Chemistry 809	Me	H	[495]
500	I	Chemistry 813	Chemistry 814	Me	H	203
501	I	Chemistry 818	Chemistry 819	Me	H	204



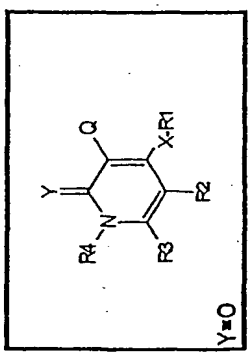
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
502	I	 Chemistry 823	 Chemistry 824	 Me	H	168
503	I	 Chemistry 828	 Chemistry 829	Me	H	217
504	I	 Chemistry 833	 Chemistry 834	Me	H	200
505	Me	 Chemistry 838	 CH2Cl	Me	H	
506	Me	 Chemistry 843	 Chemistry 844	Me	H	206



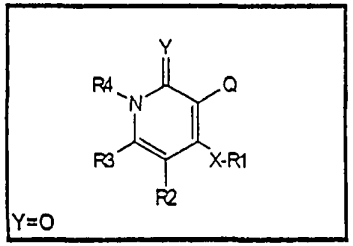
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
507	Me	Chemistry 848	CO2Et	Me	H	170
508	Me	Chemistry 853	CH2OH	Me	H	218
509	Me	Chemistry 858	Chemistry 859	Me	H	200
510	I	Chemistry 863	Chemistry 864	Me	H	166
511	I	Chemistry 868	Chemistry 869	Me	H	213

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
512	I	Chemistry 873	Chemistry 874	Me	H	[610]
513	I	Chemistry 878	CO2Et	Me	H	[751]
514	I	Chemistry 883	Chemistry 884	Me	H	[567]
515	I	Chemistry 888	Et	Me	H	[418,420]
516	I	Chemistry 893	Et	Me	H	[472]

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
517	I	Chemistry 898	Chemistry 899	Me	H	[521]
518	I	Chemistry 903	Et	Me	H	[416]
519	I	Chemistry 908	Chemistry 909	Me	H	[556]
520	I	Chemistry 913	Et	Me	H	[452,454,456]
521	I	Chemistry 918	Et	Me	H	[434,436]



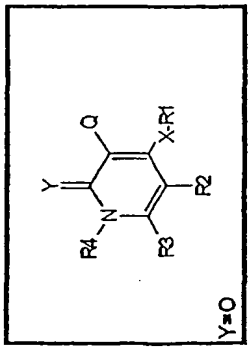
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
622	I	Chemistry 923	Et	Me	H	[476]
623	I	Chemistry 928	Chemistry 929	Me	H	[517]
624	Chemistry 932	Chemistry 933	Et	Me	H	[362]
625	Chemistry 937	Chemistry 938	Et	Me	H	[361]
626	I	Chemistry 943	Chemistry 944	Me	H	[450]



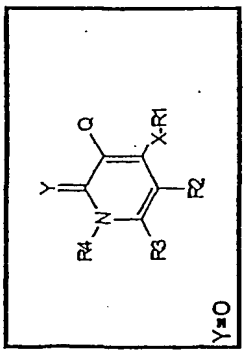
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
527	I	Chemistry 948	Et	Me	H	[399]
528	I	Chemistry 953	Et	Me	H	[381]
529	I	Chemistry 958	Chemistry 959	Me	H	[282]
530	I	Chemistry 963	Chemistry 964	Me	H	210
531	I	Chemistry 968	Chemistry 969	Me	H	144
532	I	Chemistry 973	CH2OH	Me	H	[512]

N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
533	I	Chemistry 978	Chemistry 979	Me	H	[579]
534	I	Chemistry 983	Chemistry 984	Me	H	[469]
535	I	Chemistry 988	Chemistry 989	Me	H	[485]
536	I	Chemistry 993	Et	Me	H	[380]
537	I	Chemistry 998	Et	Me	H	[424]
538	I	Chemistry 1003	Chemistry 1004	Me	H	[494]

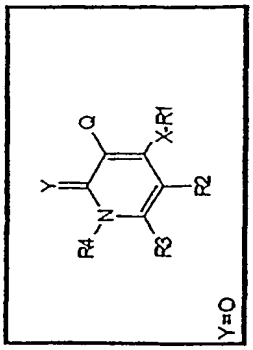
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
539	I	Chemistry 1008	Chemistry 1009	Me	H	203
540	I	Chemistry 1013	Chemistry 1014	Me	H	230
541	I	Chemistry 1018	Chemistry 1019	Me	H	[510]
542	Me	Chemistry 1023	Chemistry 1024	Me	H	206
543	Me	Chemistry 1028	Chemistry 1029	Me	H	>250

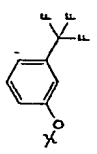
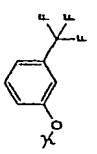
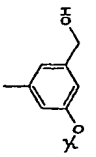
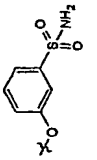
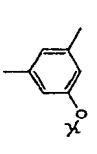
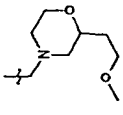


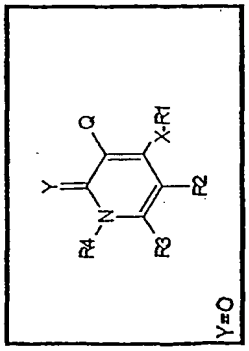
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
544	I	Chemistry 1033	Chemistry 1034	Me	H	[560,562,564]
545	I	Chemistry 1038	Chemistry 1039	Me	H	248
546	I	Chemistry 1043	Chemistry 1044	Me	H	100
547	I	Chemistry 1048	Chemistry 1049	Me	H	220
548	I	Chemistry 1053	Et	Me	H	[459]



N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
549	I	Chemistry 1058	Et	Me	H	[431]
550	I	Chemistry 1063	Et	Me	H	[398]
551	I	Chemistry 1068	Et	Me	H	[421]
552	CO2Et	Chemistry 1073	Et	Me	H	[370]
553	H	Chemistry 1078	Et	Me	H	[298]

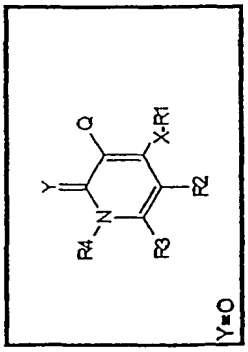


N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
554	I	 Chemistry 1083	 Et	Me	H	[424]
555	Br	 Chemistry 1088	 Et	Me	H	[376,378]
556	I	 Chemistry 1093	 Et	 Me	H	[600]
557	I	 Chemistry 1098	 Et	 Me	H	[436]
558	I	 Chemistry 1103	 Chemistry 1104	 Me	H	194

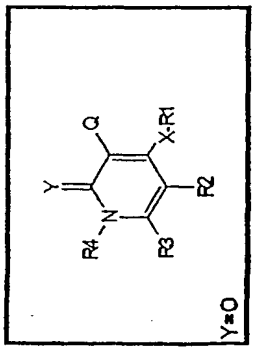


N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
559	I	Chemistry 1108	Chemistry 1109	Me	H	146
560	I	Chemistry 1113	Chemistry 1114	Me	H	168
561	I	Chemistry 1118	Chemistry 1119	Me	H	>250
562	I	Chemistry 1123	Chemistry 1124	Me	H	
563	I	Chemistry 1128	Chemistry 1129	Me	H	232

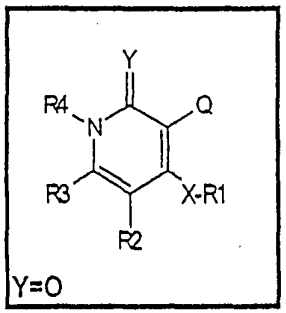
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
564	I	Chemistry 1133	Chemistry 1134	Me	H	>250
565	H	Chemistry 1138	CO2Et	Chemistry 1140	H	235
566	I	Chemistry 1143	Chemistry 1144	Me	H	210
567	Vinyl	Chemistry 1148	Chemistry 1149	Me	H	202
568	H	Chemistry 1153	Chemistry 1154	Me	H	[330]



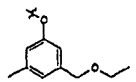
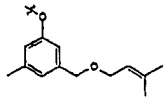
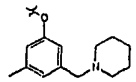
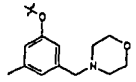
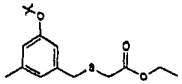
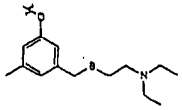
N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
569	H	Chemistry 1168	CH2CH2CO2H	Me	H	[302]
570	H	Chemistry 1163	Chemistry 1164	Me	H	[371]
571	I	Chemistry 1168	Chemistry 1169	Me	H	>250
572	I	Chemistry 1173	Chemistry 1174	Me	H	230
573	I	Chemistry 1178	Chemistry 1179	Me	H	249

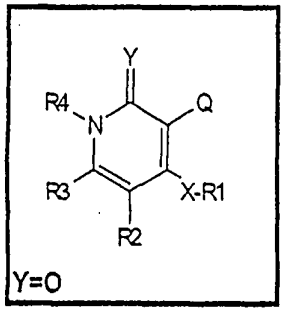


N°=	Q	X-R1	R2	R3	R4	mp.°C / (MH+)
574	I	Chemistry 1183	Chemistry 1184	Me	H	>250
575	I	Chemistry 1188	Chemistry 1189	Me	H	216
576	I	Chemistry 1193	Chemistry 1194	Me	H	>250
577	I	Chemistry 1198	Et	Me	H	[472]

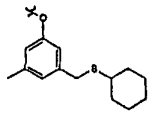
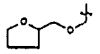
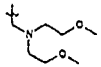


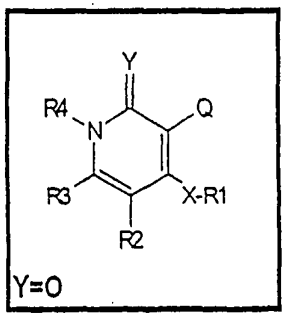
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
578	I	 Chemistry 3	 Et	Me	H	[427]
579	I	 Chemistry 8	 Et	Me	H	[468]
580	I	 Chemistry 13	 Et	Me	H	[467]
581	I	 Chemistry 18	 Et	Me	H	[469]
582	I	 Chemistry 23	 Et	Me	H	[502]
583	I	 Chemistry 28	 Et	Me	H	[515]



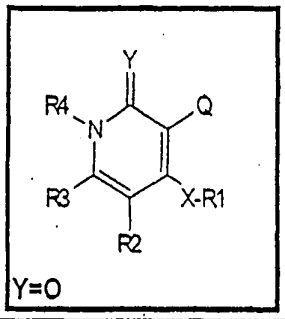
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
584	I	 Chemistry 33	 Et	Me	H	[498]
585	I	 Chemistry 38	 Chemistry 39	Me	H	180
586	I	 Chemistry 43	 Chemistry 44	Me	H	168
587	I	 Chemistry 48	 Chemistry 49	Me	H	236
588	I	 Chemistry 53	 Chemistry 54	Me	H	228
589	I	 Chemistry 58	 Chemistry 59	Me	H	>250



Y=O

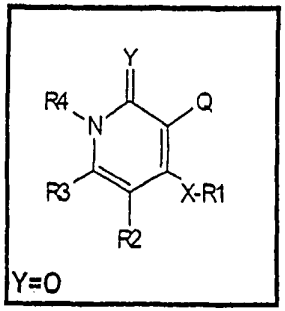
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
590	H	Chemistry 63	Chemistry 64	Me	H	[399]
591	I	Chemistry 68	Chemistry 69	Me	H	144
592	I	Chemistry 73	Chemistry 74	Me	H	>250
593	I	Chemistry 78	Chemistry 79	Me	H	192
594	I	Chemistry 83	Chemistry 84	Me	H	212



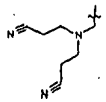
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
595	I	 Chemistry 88	 Chemistry 89	Me	H	>250
596	I	 Chemistry 93	 Chemistry 94	Me	H	[466]
597	I	 Chemistry 98	 Chemistry 99	Me	H	>250
598	Chemistry 102	 Chemistry 103	 H	Me	H	[227]
599	Chemistry 107	 Chemistry 108	 H	Me	H	[255]
600	Chemistry 112	 Chemistry 113	 H	Me	H	[244]

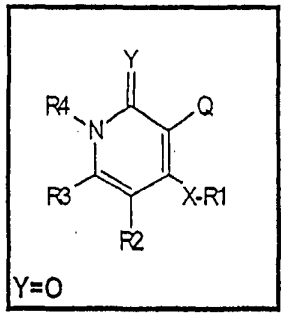
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
601	Chemistry 117	Chemistry 118	H	Me	H	[291]]
602	I	Chemistry 123	Et	Me	H	[508]
603	I	Chemistry 128	Et	Me	H	[427]
604	I	Chemistry 133	Et	Me	H	[429]
605	I	Chemistry 138	Chemistry 139	Me	H	178



Y=O

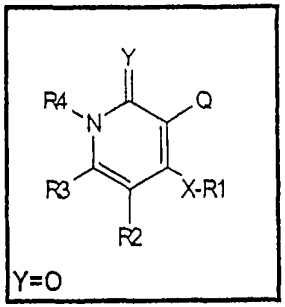
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
606	I	 Chemistry 143	 Chemistry 144	Me	H	120
607	I	 Chemistry 148	 Chemistry 149	Me	H	>250
608	I	 Chemistry 153	 Chemistry 154	Me	H	[437]
609	I	 Chemistry 158	 Chemistry 159	Me	H	[439]
610	I	 Chemistry 163	 Chemistry 164	Me	H	[426]
611	I	 Chemistry 168	 Chemistry 169	Me	H	>250

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
612	H	Chemistry 173	CO2Et	Me	H	[302]
613	Br	Chemistry 178	CO2Et	Me	H	[381]
614	Br	Chemistry 183	CH2OH	Me	H	[338,340]
615	Br	Chemistry 188	CH2Cl	Me	H	
616	Br	Chemistry 193	Chemistry 194	Me	H	>250
617	I	Chemistry 198	Chemistry 199	Me	H	>250

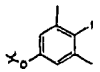
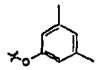
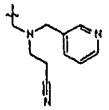
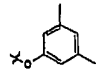
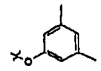
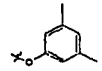
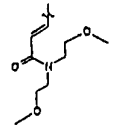


Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
618	I	Chemistry 203	Chemistry 204	Me	H	[451]
619	I	Chemistry 208	Chemistry 209	Me	H	[513]
620	I	Chemistry 213	Chemistry 214	Me	H	[639]
621	I	Chemistry 218	Chemistry 219	Me	H	[456]
622	I	Chemistry 223	Chemistry 224	Me	H	[582]
623	I	Chemistry 228	CH2CH2CO2H	Me	H	[428]

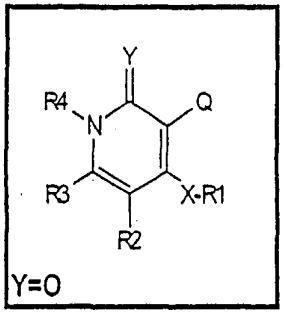


Y=O

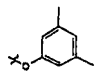
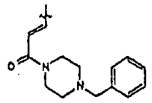
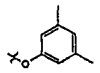
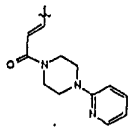
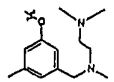
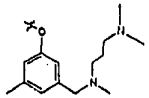
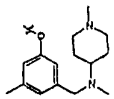
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
624	I	 Chemistry 233	 CH2CH2CO2H	Me	H	[554]
625	I	 Chemistry 238	 Chemistry 239	Me	H	[529]
626	I	 Chemistry 243	 Chemistry 244	Me	H	[453]
627	I	 Chemistry 248	 Chemistry 249	Me	H	[481]
628	I	 Chemistry 253	 Chemistry 254	Me	H	[541]

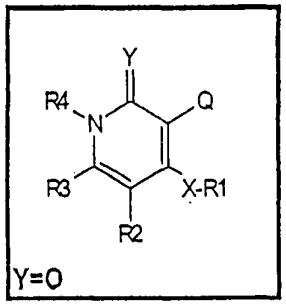
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
629	I	Chemistry 258	Chemistry 259	Me	H	[510]
630	I	Chemistry 263	Chemistry 264	Me	H	[483]
631	I	Chemistry 268	Chemistry 269	Me	H	[478]
632	I	Chemistry 273	Chemistry 274	Me	H	[492]
633	I	Chemistry 278	Chemistry 279	Me	H	[586]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
634	I	Chemistry 283	Chemistry 284	Me	H	[493]
635	I	Chemistry 288	Chemistry 289	Me	H	[536]
636	I	Chemistry 293	Chemistry 294	Me	H	[511]
637	I	Chemistry 298	Chemistry 299	Me	H	[523]
638	I	Chemistry 303	Chemistry 304	Me	H	[508]

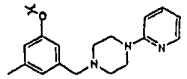
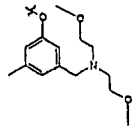
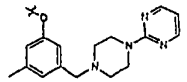
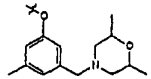


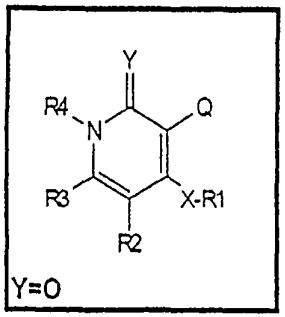
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
639	I	 Chemistry 308	 Chemistry 309	Me	H	[584]
640	I	 Chemistry 313	 Chemistry 314	Me	H	[571]
641	I	 Chemistry 318	 Et	Me	H	[484]
642	I	 Chemistry 323	 Et	Me	H	[498]
643	I	 Chemistry 328	 Et	Me	H	[510]

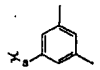
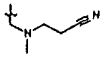
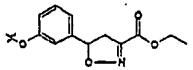
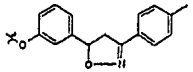
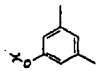


Y=O

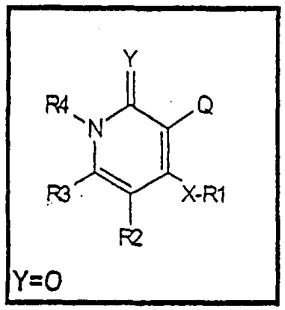
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
644	I	 Chemistry 333	 Et	Me	H	[545]
645	I	 Chemistry 338	 Et	Me	H	[514]
646	I	 Chemistry 343	 Et	Me	H	[546]
647	I	 Chemistry 348	 Et	Me	H	[497]
648	I	 Chemistry 353	 Chemistry 354	Me	H	>250
649	I	 Chemistry 358	 Chemistry 359	Me	H	165



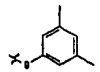
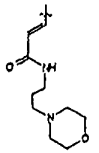
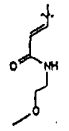
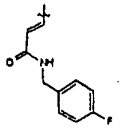
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
650	I	 Chemistry 363	 Chemistry 364	Me	H	181
651	I	 Chemistry 368	 Et	Me	H	[497]
652	I	 Chemistry 373	 Et	Me	H	[515]
653	I	 Chemistry 378	 NHCO2Et	Me	H	[443]
654	I	 Chemistry 383	 Et	Me	H	[371]
655	H	 Chemistry 388	 Et	Me	H	[245]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
656	I	Chemistry 393	Et	Me	H	[386]
657	I	Chemistry 398	Et	Me	H	[401]
658	I	Chemistry 403	Et	Me	H	[386]
659	I	Chemistry 408	Et	Me	H	[506]
660	Br	Chemistry 413	Chemistry 414	Me	H	>250
661	Br	Chemistry 418	Chemistry 419	Me	H	>250



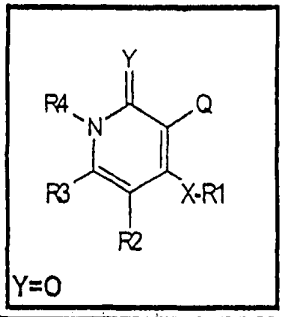
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
662	I	 Chemistry 423	 Chemistry 424	Me	H	>250
663	I	 Chemistry 428	 Chemistry 429	Me	H	[552]
664	I	 Chemistry 433	 Chemistry 434	Me	H	[483]
665	I	 Chemistry 438	 Chemistry 439	Me	H	[533]

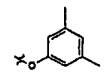
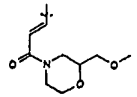
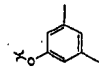
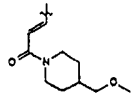
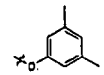
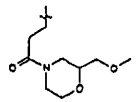
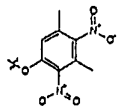
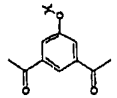
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
666	I	Chemistry 443	Chemistry 444	Me	H	[559]
667	I	Chemistry 448	Chemistry 449	Me	H	[516]
668	I	Chemistry 453	Chemistry 454	Me	H	[516]
669	I	Chemistry 458	Chemistry 459	Me	H	[505]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
670	I	Chemistry 463	Chemistry 464	Me	H	[497]
671	I	Chemistry 468	Chemistry 469	Me	H	[513]
672	I	Chemistry 473	Chemistry 474	Me	H	[588]
673	I	Chemistry 478	Chemistry 479	Me	H	[558]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
674	I	Chemistry 483	Chemistry 484	Me	H	[465]
675	I	Chemistry 488	Chemistry 489	Me	H	[559]
676	I	Chemistry 493	Chemistry 494	Me	H	[521]
677	I	Chemistry 498	Chemistry 499	Me	H	[525]

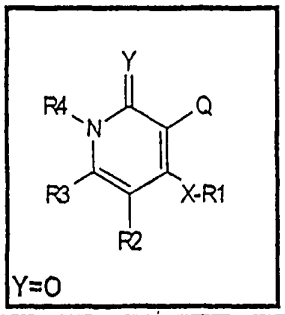


Y=O

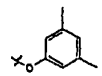
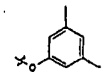
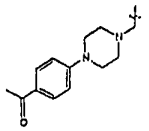
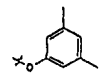
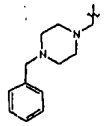
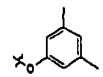
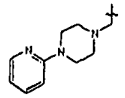
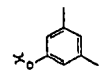
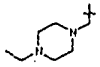
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
678	I	 Chemistry 503	 Chemistry 504	Me	H	>250
679	I	 Chemistry 508	 Chemistry 509	Me	H	>250
680	I	 Chemistry 513	 Chemistry 514	Me	H	>250
681	H	 Chemistry 518	 CO2Et	Me	H	[392]
682	I	 Chemistry 523	 Et	Me	H	[440]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
683	I	Chemistry 528	Et	Me	H	[492]
684	I	Chemistry 533	Et	Me	H	[486]
685	I	Chemistry 538	Et	Me	H	[412]
686	I	Chemistry 543	Et	Me	H	[414]
687	I	Chemistry 548	Et	Me	H	[398]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
688	H	Chemistry 553	Et	Me	H	[272]
689	CO2Et	Chemistry 558	Et	Me	H	[344]
690	H	Chemistry 563	Et	Me	H	[272]
691	I	Chemistry 568	Chemistry 569	Me	H	[471]
692	I	Chemistry 573	Et	Me	H	[531]

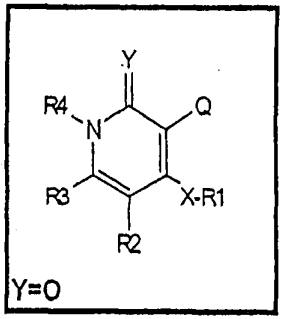


Y=O

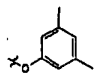
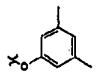
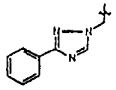
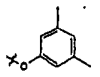
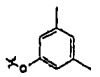
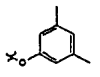
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
693	I	 Chemistry 578	 Chemistry 579	Me	H	[468]
694	I	 Chemistry 583	 Chemistry 584	Me	H	[572]
695	I	 Chemistry 588	 Chemistry 589	Me	H	[544]
696	I	 Chemistry 593	 Chemistry 594	Me	H	[531]
697	I	 Chemistry 598	 Chemistry 599	Me	H	[482]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
698	I	Chemistry 603	Chemistry 604	Me	H	[557]
699	I	Chemistry 608	Chemistry 609	Me	H	[598,600,602]
700	I	Chemistry 613	Chemistry 614	Me	H	[548]
701	I	Chemistry 618	Chemistry 619	Me	H	[496]
702	I	Chemistry 623	Chemistry 624	Me	H	[532]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
703	I	Chemistry 628	Chemistry 629	Me	H	[544]
704	I	Chemistry 633	Chemistry 634	Me	H	>250
705	I	Chemistry 638	Chemistry 639	Me	H	[530]
706	I	Chemistry 643	Chemistry 644	Me	H	[450]
707	I	Chemistry 648	Chemistry 649	Me	H	[542,544]

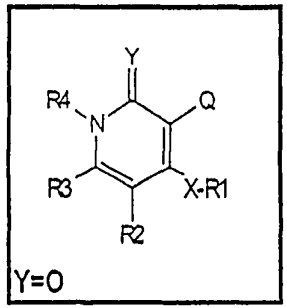


Y=O

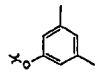
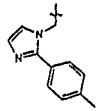
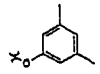
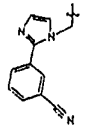
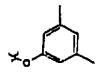
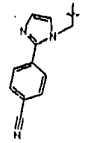
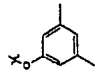
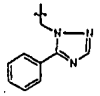
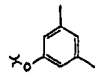
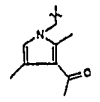
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
708	I	 Chemistry 653	 Chemistry 654	Me	H	[514,516]
709	I	 Chemistry 658	 Chemistry 659	Me	H	[528,530]
710	I	 Chemistry 663	 Chemistry 664	Me	H	[513]
711	I	 Chemistry 668	 Chemistry 669	Me	H	[438]
712	I	 Chemistry 673	 Chemistry 674	Me	H	[451]
713	I	 Chemistry 678	 Chemistry 679	Me	H	[437]

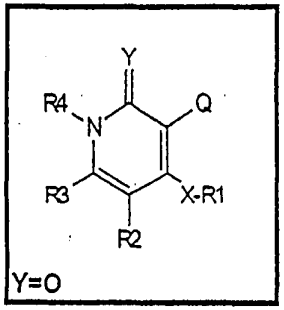
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
714	I	Chemistry 683	Chemistry 684	Me	H	[465]
715	I	Chemistry 688	Chemistry 689	Me	H	[513]
716	I	Chemistry 693	Chemistry 694	Me	H	[530]
717	I	Chemistry 698	Chemistry 699	Me	H	[512]
718	I	Chemistry 703	Chemistry 704	Me	H	[450]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
719	I	Chemistry 708	Chemistry 709	Me	H	[466]
720	I	Chemistry 713	Chemistry 714	Me	H	[512]
721	I	Chemistry 718	Chemistry 719	Me	H	[464]
722	I	Chemistry 723	Chemistry 724	Me	H	[478]
723	I	Chemistry 728	Chemistry 729	Me	H	[450]

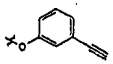
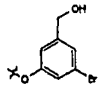
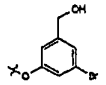
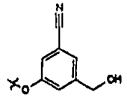
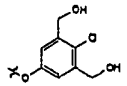
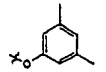


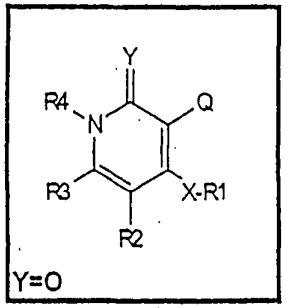
Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
724	I	 Chemistry 733	 Chemistry 734	Me	H	[526]
725	I	 Chemistry 738	 Chemistry 739	Me	H	[537]
726	I	 Chemistry 743	 Chemistry 744	Me	H	[537]
727	I	 Chemistry 748	 Chemistry 749	Me	H	>250
728	I	 Chemistry 753	 Chemistry 754	Me	H	164

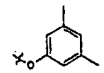
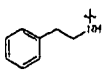
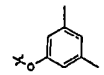
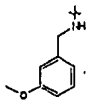
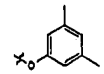
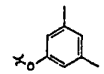


Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
729	H	 Chemistry 758	 Et	Me	H	[254]
730	I	 Chemistry 763	 Et	Me	H	[464,466]
731	H	 Chemistry 768	 Et	Me	H	[338,340]
732	H	 Chemistry 773	 Et	Me	H	[285]
733	I	 Chemistry 778	 Et	Me	H	[450,451]
734	I	 Chemistry 783	 NH2	Me	H	[371]

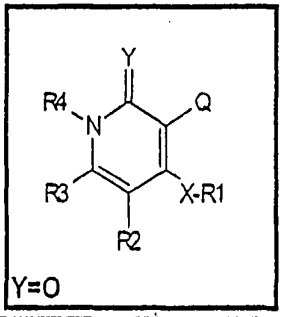


Y=O

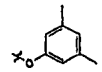
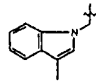
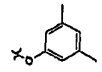
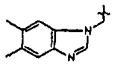
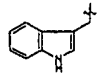
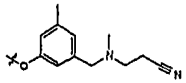
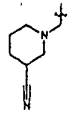
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
735	I	 Chemistry 788	 Chemistry 789	Me	H	[475]
736	I	 Chemistry 793	 Chemistry 794	Me	H	[491]
737	I	 Chemistry 798	 NMe2	Me	H	[399]
738	CO2Et	 Chemistry 803	 Et	Me	H	[428]
739	I	 Chemistry 808	 Chemistry 809	Me	H	[461]
740	I	 Chemistry 813	 Chemistry 814	Me	H	248

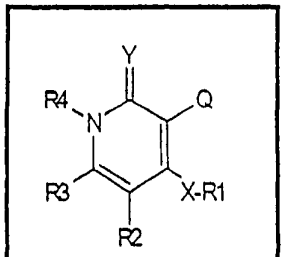
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
741	I	Chemistry 818	Chemistry 819	Me	H	>250
742	I	Chemistry 823	Chemistry 824	Me	H	[486]
743	I	Chemistry 828	Chemistry 829	Me	H	[504,506,508]
744	I	Chemistry 833	Chemistry 834	Me	H	[513]
745	I	Chemistry 838	Chemistry 839	Me	H	[562

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
746	I	Chemistry 843	Chemistry 844	Me	H	[563]
747	I	Chemistry 848	Chemistry 849	Me	H	[527]
748	I	Chemistry 853	Chemistry 854	Me	H	[563,565]
749	I	Chemistry 858	Chemistry 859	Me	H	[486]
750	I	Chemistry 863	Chemistry 864	Me	H	[515]
751	I	Chemistry 868	Chemistry 869	Me	H	[500]

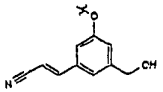
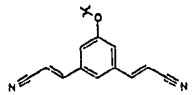


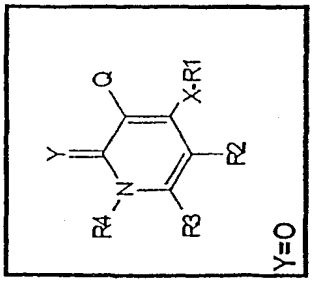
Y=O

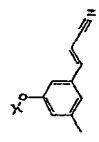
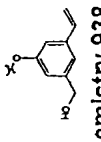
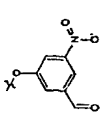
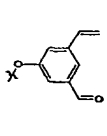
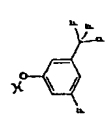
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
752	I	 Chemistry 873	 Chemistry 874	Me	H	[499]
753	I	 Chemistry 878	 Chemistry 879	Me	H	[514]
754	I	 Chemistry 883	 Chemistry 884	Me	H	>250
755	I	 Chemistry 888	 Et	Me	H	[466]
756	I	 Chemistry 893	 Chemistry 894	Me	H	[478]
757	I	 Chemistry 898	 Chemistry 899	Me	H	>250

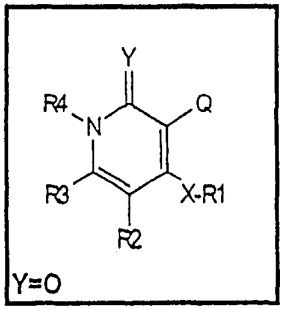


Y=O

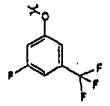
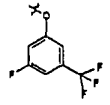
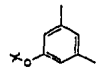
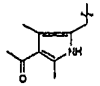
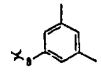
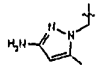
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
758	I	 Chemistry 903	 Chemistry 904	Me	H	>250
759	I	 Chemistry 908	 Chemistry 909	Me	H	213
760	I	 Chemistry 913	 Chemistry 914	Me	H	207
761	I	 Chemistry 918	 Chemistry 919	Me	H	>250
762	I	 Chemistry 923	 Et	Me	H	[437]
763	I	 Chemistry 928	 Et	Me	H	[458]

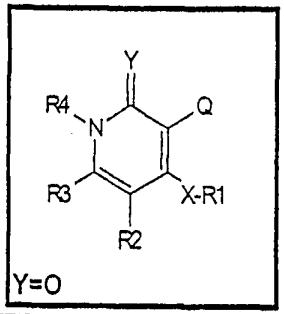


N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
764	Vinyl	 Chemistry 933	 Et	Me	H	[321]
765	H	 Chemistry 938	Et	Me	H	[286]
766	I	 Chemistry 943	Et	Me	H	[429]
767	H	 Chemistry 948	Et	Me	H	[284]
768	CO2Et	 Chemistry 953	Et	Me	H	[388]

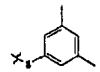
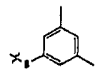
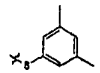
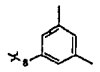
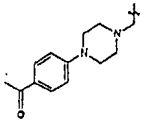
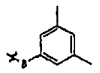
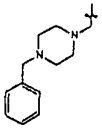


Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
769	H	 Chemistry 958	 Et	Me	H	[316]
770	I	 Chemistry 963	 Et	Me	H	[442]
771	CO2Et	 Chemistry 968	 Et	Me	H	[380,382]
772	H	 Chemistry 973	 Et	Me	H	[308,310]
773	I	 Chemistry 978	 Chemistry 979	Me	H	>250
774	I	 Chemistry 983	 Chemistry 984	Me	H	[481]



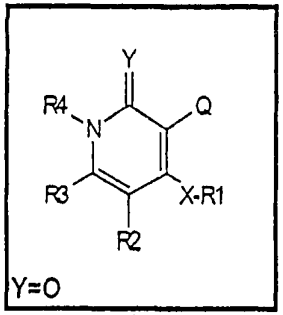
Y=O

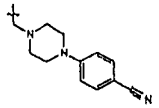
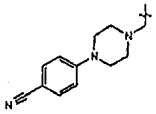
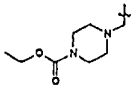
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
775	I	 Chemistry 988	 Chemistry 989	Me	H	[545]
776	I	 Chemistry 993	 Chemistry 994	Me	H	[476]
777	I	 Chemistry 998	 Chemistry 999	Me	H	[484]
778	I	 Chemistry 1003	 Chemistry 1004	Me	H	[588]
779	I	 Chemistry 1008	 Chemistry 1009	Me	H	[560]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
780	I	Chemistry 1013	Chemistry 1014	Me	H	[547]
781	I	Chemistry 1018	Chemistry 1019	Me	H	[591]
782	I	Chemistry 1023	Chemistry 1024	Me	H	[580]
783	I	Chemistry 1028	Chemistry 1029	Me	H	[546]
784	I	Chemistry 1033	Chemistry 1034	Me	H	[574]

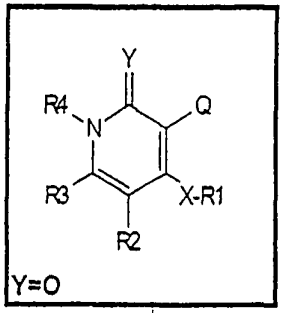
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
785	I	Chemistry 1038	Chemistry 1039	Me	H	[614,616,618]
786	I	Chemistry 1043	Chemistry 1044	Me	H	[564]
787	I	Chemistry 1048	Chemistry 1049	Me	H	[548]
788	I	Chemistry 1053	Chemistry 1054	Me	H	[552]
789	I	Chemistry 1058	Chemistry 1059	Me	H	[560]

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
790	I	Chemistry 1063	Chemistry 1064	Me	H	[586]
791	I	Chemistry 1068	Chemistry 1069	Me	H	[530,532]
792	I	Chemistry 1073	Chemistry 1074	Me	H	[604]
793	I	Chemistry 1078	Chemistry 1079	Me	H	[580]
794	I	Chemistry 1083	Chemistry 1084	Me	H	[493]
795	H	Chemistry 1088	CH2OH	Me	H	[260]

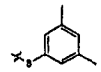
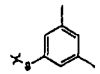
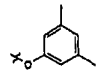
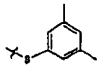
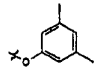
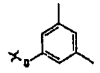


N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
796	H	 Chemistry 1093	 CH2Cl	Me	H	
797	H	 Chemistry 1098	 Chemistry 1099	Me	H	>250
798	I	 Chemistry 1103	 Chemistry 1104	Me	H	245
799	I	 Chemistry 1108	 Chemistry 1109	Me	H	>250
800	I	 Chemistry 1113	 Chemistry 1114	Me	H	232

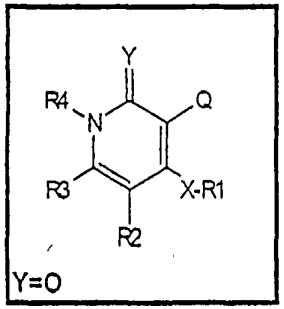
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
801	I	Chemistry 1118	Chemistry 1119	Me	H	224
802	I	Chemistry 1123	Chemistry 1124	Me	H	184
803	I	Chemistry 1128	Chemistry 1129	Me	H	>250
804	I	Chemistry 1133	Chemistry 1134	Me	H	>250
805	I	Chemistry 1138	Chemistry 1139	Me	H	>250



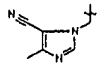
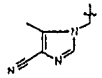
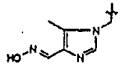
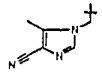
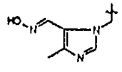
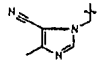
Y=O

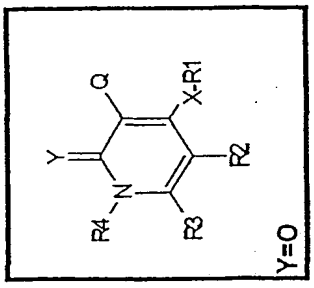
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
806	I	 Chemistry 1143	 Chemistry 1144	Me	H	>250
807	I	 Chemistry 1148	 Chemistry 1149	Me	H	250
808	I	 Chemistry 1153	 Chemistry 1154	Me	H	198
809	NO2	 Chemistry 1158	 CO2Et	Me	H	[363]
810	NH2	 Chemistry 1163	 CO2Et	Me	H	[317]
811	NMe2	 Chemistry 1168	 CO2Et	Me	H	[361]

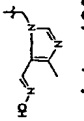
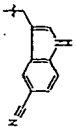
N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
812	NMe2	Chemistry 1173	CH2OH	Me	H	146
813	NMe2	Chemistry 1178	CH2Cl	Me	H	[337]
814	NMe2	Chemistry 1183	Chemistry 1184	Me	H	178
815	NMe2	Chemistry 1188	Chemistry 1189	Me	H	168
816	I	Chemistry 1193	Chemistry 1194	Me	H	[493]
817	I	Chemistry 1198	Chemistry 1199	Me	H	[493]



Y=O

N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
818	I	 Chemistry 1203	 Chemistry 1204	Me	H	>250
819	I	 Chemistry 1208	 Chemistry 1209	Me	H	>250
820	I	 Chemistry 1213	 Chemistry 1214	Me	H	[509]
821	I	 Chemistry 1218	 Chemistry 1219	Me	H	>250
822	I	 Chemistry 1223	 Chemistry 1224	Me	H	>250
823	I	 Chemistry 1228	 Chemistry 1229	Me	H	>250



N°=	Q	X-R1	R2	R3	R4	mp.°C /(MH+)
824	I	 Chemistry 1233	 Chemistry 1234	Me	H	>250
825	I	 Chemistry 1238	 Chemistry 1239	Me	H	>250

A rapid, sensitive and automated assay procedure was used for the in vitro evaluation of anti-HIV agents. An HIV-1 transformed T4-cell line, MT-4, which was previously shown (Koyanagi *et al.*, *Int. J. Cancer*, (1985), **36**, 445-451) to be highly susceptible to and permissive for HIV infection, served as the target cell line. Inhibition of the HIV-induced cytopathic effect was used as the end point. The viability of both HIV- and mock-infected cells was assessed spectrophotometrically via the *in situ* reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The 50% cytotoxic concentration (CC_{50} in μM) was defined as the concentration of compound that reduced the absorbance of the mock-infected control sample by 50%. The percent protection achieved by the compound in HIV-infected cells was calculated by the following formula :

$$\frac{(OD_T)_{HIV} - (OD_C)_{HIV}}{(OD_C)_{MOCK} - (OD_C)_{HIV}}$$

expressed in %,

whereby $(OD_T)_{HIV}$ is the optical density measured with a given concentration of the test compound in HIV-infected cells; $(OD_C)_{HIV}$ is the optical density measured for the control untreated HIV-infected cells; $(OD_C)_{MOCK}$ is the optical density measured for the control untreated mock-infected cells; all optical density values were determined at 540 nm. The dose achieving 50% protection according to the above formula was defined as the 50% inhibitory concentration (IC_{50} in μM). The ratio of CC_{50} to IC_{50} was defined as the selectivity index (SI). The compounds of formula (I) were shown to inhibit HIV-1 effectively. Particular IC_{50}, CC_{50} and SI values are listed in Table 2 hereinbelow.

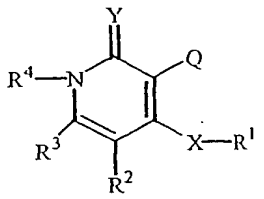
Table 2

N°	IC50(µm)	c	SI	c	CC50(µm)
242	0,0006	>	158489	>	100
255	0,0006	>	15849	>	10
684	0,0008	>	125893	>	100
43	0,0010		10000		10
264	0,0010	>	10000	>	10
470	0,0010		12589		13
483	0,0010	>	100000	>	100
551	0,0010		12589		13
124	0,0013	>	7943	>	10
249	0,0013	>	25119	>	32
298	0,0013	>	7943	>	10
326	0,0013		7943		10
375	0,0013	>	79433	>	100
589	0,0013	>	7943	>	10
606	0,0013		15849		20
133	0,0016	>	6310	>	10
241	0,0016	>	63096	>	100
253	0,0016	>	6310	>	10
306	0,0016	>	19953	>	32
328	0,0016	>	63096	>	100
370	0,0016	>	63096	>	100
662	0,0016	>	63096	>	100
426	0,0016		39811		63
46	0,0020	>	50119	>	100
105	0,0020	>	5012	>	10
234	0,0020		5012		10
254	0,0020	>	15849	>	32
256	0,0020	>	5012	>	10
272	0,0020		12589		25
284	0,0020	>	5012	>	10
296	0,0020		12589		25
319	0,0020	>	50119	>	100
574	0,0020	>	50119	>	100
618	0,0020		25119		50
650	0,0020	>	50119	>	100
83	0,0025		3162		8
88	0,0025	>	39811	>	100
108	0,0025		19953		50
109	0,0025		12589		32
115	0,0025		3162		8

277	0,0025	>	39811	>	100
286	0,0025	>	12589	>	32
299	0,0025		32		0
713	0,0025	>	39811	>	100
45	0,0032	>	31623	>	100
85	0,0032	>	31623	>	100
86	0,0032	>	31623	>	100
231	0,0032		3162		10
409	0,0032		12589		40
244	0,0040	>	25119	>	100
297	0,0040	>	7943	>	32
250	0,0050		5012		25
257	0,0050	>	6310	>	32
307	0,0050	>	6310	>	32
324	0,0050		6310		32
81	0,0063		1995		13
92	0,0063	>	5012	>	32
140	0,0063	>	1585	>	10
143	0,0063	>	1585	>	10
217	0,0063	>	1585	>	10
221	0,0063	>	3162	>	20
230	0,0063		1259		8
232	0,0063	>	5012	>	32
245	0,0063	>	15849	>	100
309	0,0063		1585		10
321	0,0063	>	15849	>	100
322	0,0063	>	15849	>	100
547	0,0063	>	15849	>	100
31	0,0079	>	12589	>	100
218	0,0079	>	1259	>	10
222	0,0079		251		2
700	0,0079	>	1000	>	8
314	0,0079	>	3981	>	32
701	0,0100		6310		63
8	0,0100	>	10000	>	100
99	0,0100	>	10000	>	100
121	0,0100	>	10000	>	100
219	0,0100	>	3162	>	32
233	0,0100	>	1000	>	10
694	0,0100		39811		63
280	0,0100		2512		25
696	0,0158	>	2512	>	40

CLAIMS

1. Compounds of formula (I)



(I),

the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and stereochemically isomeric forms thereof, wherein

Y is O or S;

Q is hydrogen; halo; C_{1-6}alkyl; di(C_{1-4}alkyl)amino; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkylthioC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-S(=O)-; C_{1-6}alkyl-S(=O)$_2$-; hydroxyC_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkylthio; aminocarbonyl$_6C_{1-6}$alkylthio; C_{1-6}alkyloxyC_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, -COOH, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{3-6}cycloalkyl optionally substituted with C_{1-4}alkyl; cyano; carboxyl; formyl; R^5R^6N-C(=O)-; R^5R^6N-C(=O)-C_{1-6}alkyl; *N*-hydroxy-imino; *N*-C_{1-4}alkyloxy-imino; aryl; aryloxy; arylthio; arylC_{1-6}alkyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with hydroxy or aryl; Het^1; Het^1oxy; Het^1thio; Het^1C_{1-6}alkyl; Het^1carbonyl; Het^1C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-P(OR^{15})$_2$=O or C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O;

X is a bivalent radical of formula

-$(CH_2)_p$- (a-1) or

-$(CH_2)_q$-Z-$(CH_2)_r$- (a-2);

wherein p is an integer of value 1 to 5;

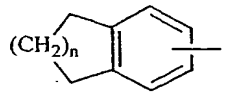
q is an integer of value 0 to 5;

r is an integer of value 0 to 5;

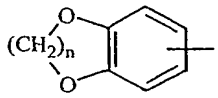
Z is O, S, NR^7, C(=O), S(=O), S(=O)$_2$, $CHOR^{13}$, CH=CH, $CH(NR^7R^8)$ or CF_2;

and wherein each hydrogen atom may be replaced by C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkenyl, C_{1-6}alkoxy, aryl or a monocyclic or bicyclic heterocycle selected from pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, or a radical of formula


(b-1)

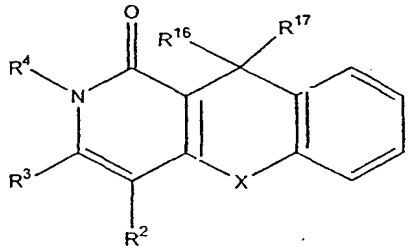
or


(b-2)

with n being an integer of 1 or 2,

said monocyclic or bicyclic heterocycle or said radical of formula (b-1) or (b-2) optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, polyhaloC_{1-4}alkyl or phenyl;

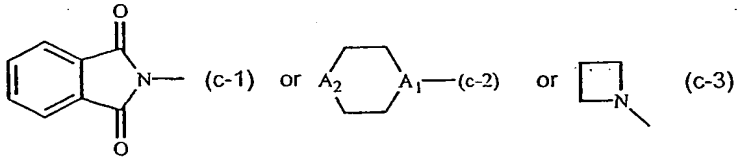
or Q and X-R^1 may be taken together with the pyridinone to form a tricyclic heterocycle of formula


(h-1)

with R^{16} and R^{17} being C_{1-6}alkyl or forming together =O.

R^2 and R^3 each independently are selected from hydrogen; halo; formyl; cyano; azido; hydroxy; oxiranyl; amino; mono- or di(C_{1-4}alkyl)amino; formylamino; mercapto(C_{1-6})alkyl; hydrazino; $R^{5a}R^{6a}$N-C(=O)-; R^9-N=C(R^{10})-; C_{2-6}alkenyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, di(C_{1-4}alkyl)carbamoyl, [di(C_{1-4}alkyl)amino(C_{1-6}alkyl)](C_{1-4}alkyl)carbamoyl, [di(C_{1-4}alkyl)amino(C_{1-6}alkyl)](arylC_{1-4}alkyl)carbamoyl, di(C_{1-4}alkyloxy)(C_{1-4}alkyl)carbamoyl, (cyanoC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N*-hydroxy-imino, aryl, Het^2, Het^2carboxamido, Het^2(C_{1-6}alkyl)carbamoyl; C_{2-6}alkynyl optionally substituted with one or two substituents each independently selected

from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{1-6}alkyloxy; hydroxyC_{1-6}alkyloxy; aminoC_{1-6}alkyloxy; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; arylcarbonyl; Het^2carbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxy; aryl; aryloxy; arylC_{1-6}alkyloxy; arylthio; arylC_{1-6}alkylthio; mono- or di(aryl)amino; Het^2; Het^2oxy; Het^2thio; Het^2C_{1-6}alkyloxy; Het^2C_{1-6}alkylthio; Het^2SO_2; Het^2SO; mono- or di(Het^2)amino; C_{3-6}cycloalkyl; C_{3-6}cycloalkyloxy; C_{3-6}cycloalkylthio; C_{1-6}alkylthio; hydroxyC_{1-6}alkylthio; aminoC_{1-6}alkylthio; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, carboxyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl, C_{1-6}alkycarbamoylC_{1-4}alkylthio, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylthio C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, aminocarbonyloxy, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonylC_{1-6}alkylthio, aryl, Het^2, aryloxy, arylthio, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, Het^2C_{1-6}alkyloxy, Het^2C_{1-6}alkylthio, C_{1-6}alkyl-S(=O)$_2$-oxy, amino, mono- or di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkylthio, [di(C_{1-6}alkyl)amino(C_{1-6}alkyl)](C_{1-6}alkyl)amino, di(cyanoC_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, C_{1-6}alkyloxyC_{1-6}alkylcarbonylamino, mono- or di(aryl)amino, mono- or di(arylC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyloxyC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkylthioC_{1-4}alkyl)amino, mono- or di(Het^2C_{1-4}alkyl)amino, (Het^2C_{1-4}alkyl)(C_{1-4}alkyl)amino, (cyanoC_{1-6}alkyl)(C_{1-6}alkyl)amino, C_{3-6}cycloalkylthio, R^{11}-(C=O)-NH-, R^{12}-NH-(C=O)-NH-, R^{14}-S(=O)$_2$-NH-, C_{1-6}alkyl-P(O-R^{15})2=O, C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O or a radical of formula



with A_1 being CH or N, and A_2 being CH_2, NR^{13}, S or O, provided that when A_1 is CH then A_2 is other than CH_2, said radical (c-1), (c-2) and (c-3) being optionally substituted with one or two substituents each independently selected from H, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6} alkyloxycarbonylC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylcarbonyl, arylcarbonyl, aryl, Het^1, Het^1-(C=0)-, hydroxy, cyano, C_{1-4}alkylcyano, $CONR^{16}R^{17}$ with R^{16}

and R^{17} being independently H or alkyl, mono or di(C_{1-4}alkyl)aminoalkyl, 4-hydroxy-4-phenyl or 4-cyano-4-phenyl;

or R^2 and R^3 may be taken together to form a bivalent radical of formula

$-(CH_2)_t-CH_2-A_3-CH_2-$ (d-1) or $-CH=CH-CH=CH-$ (d-2)

with t being an integer of 0, 1 or 2 and A_3 being CH_2, O, S, NR^{7a} or $N[C(=O)R^{8a}]$ and wherein each hydrogen in said formula (d-1) or (d-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

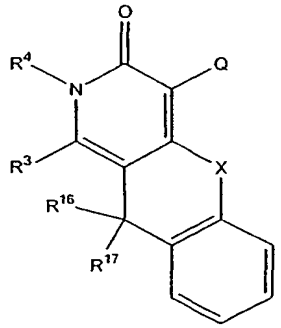
R^4 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, amino, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl or aryl;

or R^4 and R^3 may be taken together to form a bivalent radical of formula

$-(CH_2)_t-CH_2-A_4-CH_2-$ (e-1) or $-CH=CH-CH=CH-$ (e-2)

with t being an integer of 0, 1 or 2 and A_4 being CH_2, O, S, NR^{7b} or $N[C(=O)R^{8b}]$ and wherein each hydrogen in said formula (e-1) or (e-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

or X-R^1 and R^2 may be taken together to form a tricyclic heterocycle of formula

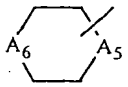


(*h*-2)

with R^{16} and R^{17} being C_{1-6}alkyl or forming together =O .

R^5 and R^6 each independently are hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^{5a} and R^{6a} each independently are hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkylthio, amino, mono-or di(C_{1-4}alkyl)amino or a radical of formula



(f-1)

with A_5 and A_6 each independently being CH_2, NR^{13} or O;

R^7, R^{7a} and R^{7b} each independently are hydrogen, formyl or C_{1-4}alkyl;

R^8, R^{8a} and R^{8b} each independently are hydrogen or C_{1-4}alkyl;

R^9 is hydrogen, hydroxy, C_{1-4}alkyloxy, carboxylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy or arylC_{1-4}alkyloxy;

R^{10} is hydrogen, carboxyl or C_{1-4}alkyl;

R^{11} is hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkyl-$S(=O)_2$-, aryl or Het^3; C_{1-4}alkyloxy; C_{2-4}alkenyl; arylC_{2-4}alkenyl; Het^3C_{2-4}alkenyl; C_{2-4}alkynyl; Het^3C_{2-4}alkynyl, arylC_{2-4}alkynyl; C_{3-6}cycloalkyl; aryl; naphthyl or Het^3;

R^{12} is C_{1-4}alkyl, arylC_{1-4}alkyl, aryl, arylcarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkyloxycarbonylC_{1-4}alkyl;

R^{13} is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

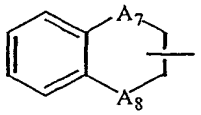
R^{14} is C_{1-4}alkyl optionally substituted with aryl or Het^4; polyhaloC_{1-4}alkyl or C_{2-4}alkenyl optionally substituted with aryl or Het^4;

R^{15} is C_{1-4} alkyl;

Het^1 and Het^2 each independently are a heterocycle selected from pyrrolyl, furanyl,

thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyrimidinyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl, morpholinyl, thiomorpholinyl triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, indolyl, indazolyl, benzodioxanyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, imidazopyridinyl, dihydropyrrolyl or dihydroisoxazolyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from O, S, halo, formyl, amino, hydroxy, cyano, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, carbamoylC_{1-4}alkyl, carbamoylC_{1-4}alkoxy, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, -$OCONH_2$, C_{1-4}alkoxyC_{1-4}alkyl, aryl, Het^2C_{1-4}alkyl , polyhaloC_{1-4}alkyl, C_{3-6}cycloalkyl or arylC_{2-6}alkenyl;

Het^3 is a monocyclic or bicyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl or a radical of formula



(g-1),

with A_7 or A_8 each independently being selected from CH_2 or O;

each of said monocyclic or bicyclic heterocycles may optionally be substituted with one, two or three substituents each independently selected from halo, hydroxy,C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^4 is a monocyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^5 is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, piperidinyl, morpholinyl or pyrrolidinyl;

aryl is phenyl optionally substituted with one, two or three substituents each independently selected from halo; hydroxy; carboxyl; cyano; formyl; acetyl; nitro; amino; mono- or di(C_{1-4}alkyl)amino; C_{1-4}alkylcarbonylamino; mono- or di(C_{1-4}alkyl)aminocarbonylamino; C_{1-4}alkyl-S(=O)$_2$-NH-; Het^5(=S)-S-C_{1-4}alkyl ; C_{1-6}alkyloxy; sulfamoyl; (C_{1-4}alkyl)sulfamoyl; arylsulfamoyl; Het^2sulfamoyl; O-P=OR^{15}; C_{1-6}alkyl optionally substituted with halo, hydroxy, cyano, nitro, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{2-6}alkenyloxy, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonylthio, *N*-hydroxyimino, phenyl or Het^5; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, nitro, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; phenyl; phenyloxy; phenyl(C_{1-4}alkyl)thioC_{1-4}alkyl; (C_{3-6})cyclohexylthioC_{1-4}alkyl or isoxazolinyl optionally substituted by C_{1-4}alkyloxycarbonyl or morpholinylC_{1-4}alkyl

provided that

5,6,7,8-tetrahydro-3-iodo-4-phenoxy-1-phenyl-2(1*H*)quinolinone;

3-iodo-6-methyl-4-phenoxy-2(1*H*)-pyridinone;

2-[(3,5,6-trifluoro-1,2-dihydro-2-oxo-4-pyridinyl)amino]benzoic acid;

1,2-dihydro-6-hydroxy-2-oxo-4-(2-phenylethyl)-3-pyridinecarbonitrile;

1,2-dihydro-6-hydroxy-2-oxo-4-(4-pyridinylmethyl)-3-pyridinecarbonitrile;

4-[(4-bromophenyl)methoxy]-3,5-diodo-1-methyl-2(1*H*)-pyridinone;

4-[(4-bromophenyl)methoxy]-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxylic acid; 1,2-dihydro-6-methyl-2-oxo-4-(phenylthio)-3-pyridinecarboxylic acid and the alkyl-4-arylthio-1,2-dihydro-5-methyl-6-methyl-2-oxo-3-pyridine carboxylate

3-bromo-4-[[[2-(3,4-dimethoxyphenyl)ethyl]amino]methyl-2(1*H*)quinolinone;

3-iodo-7-methoxy-1-methyl-4-phenoxy-2(1*H*)quinolinone;

1-ethyl-3-iodo-7-methoxy-4-phenoxy-2(1*H*)quinolinone;

3-iodo-7-methoxy-4-(4-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;

1-ethyl-3-iodo-7-methoxy-4-(4-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-(3-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
1-ethyl-3-iodo-7-methoxy-4-(3-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-phenoxy-2(1*H*)quinolinone;
4-(3-chloro-4-methoxyphenoxy)-3-iodo-7-methoxy-2(1*H*)quinolinone;
3-iodo-4-phenoxy-2(1*H*)quinolinone;
3-iodo-4-phenoxy-1-phenyl-2(1*H*)quinolinone;
3-iodo-4-(4-methylphenoxy)-2(1*H*)quinolinone;
3-iodo-4-(4-methoxyphenoxy)-2(1*H*)quinolinone;
are not included.

2. Compounds as claimed in claim 1 wherein

Q is halo; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkylthioC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-S(=O)-; C_{1-6}alkyl-S(=O)$_2$-; hydroxyC_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{3-6}cycloalkyl optionally substituted with C_{1-4}alkyl; cyano; carboxyl; formyl; R^5R^6N-C(=O)-; R^5R^6N-C(=O)-C_{1-6}alkyl; *N*-hydroxy-imino; *N*-C_{1-4}alkyloxy-imino; aryl; aryloxy; arylthio; arylC_{1-6}alkyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryl; Het^1; Het^{1}oxy; Het^{1}thio; Het$^1C_{1-6}$alkyl; Het^{1}carbonyl; Het$^1C_{1-6}$alkyloxycarbonyl; C_{1-6}alkyl-P(OR^{15})$_2$=O or C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O;

X is a bivalent radical of formula

-$(CH_2)_p$- (a-1) or

-$(CH_2)_q$-Z-$(CH_2)_r$- (a-2);

wherein p is an integer of value 1 to 5;

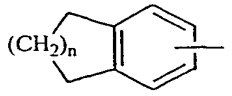
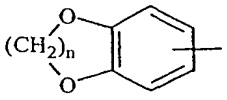
q is an integer of value 0 to 5;

r is an integer of value 0 to 5;

Z is O, S, NR^7, C(=O), S(=O), S(=O)$_2$, $CHOR^{13}$, CH=CH, $CH(NR^7R^8)$ or CF_2;

and wherein each hydrogen atom may be replaced by C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

R^1 is C_{3-6}cycloalkyl, aryl or a monocyclic or bicyclic heterocycle selected from pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, or a radical of formula

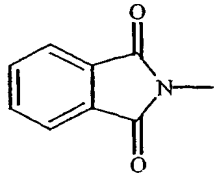
 (b-1) or  (b-2)

with n being an integer of 1 or 2,

said monocyclic or bicyclic heterocycle or said radical of formula (b-1) or (b-2) optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, polyhaloC_{1-4}alkyl or phenyl;

R^2 and R^3 each independently are selected from hydrogen; halo; formyl; cyano; azido; hydroxy; oxiranyl; amino; mono- or di(C_{1-4}alkyl)amino; formylamino; $R^{5a}R^{6a}N$-C(=O)-; R^9-N=C(R^{10})-; C_{2-6}alkenyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{2-6}alkynyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{1-6}alkyloxy; hydroxyC_{1-6}alkyloxy; aminoC_{1-6}alkyloxy; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; arylcarbonyl; Het^2carbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxy; aryl; aryloxy; arylC_{1-6}alkyloxy; arylthio; arylC_{1-6}alkylthio; mono- or di(aryl)amino; Het^2; Het^2oxy; Het^2thio; Het^2C_{1-6}alkyloxy; Het^2C_{1-6}alkylthio; mono- or di(Het^2)amino; C_{3-6}cycloalkyl; C_{3-6}cycloalkyloxy; C_{3-6}cycloalkylthio; C_{1-6}alkylthio; hydroxyC_{1-6}alkylthio; aminoC_{1-6}alkylthio; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyloxy, C_{1-6}alkylthio, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, aminocarbonyloxy, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxycarbonylC_{1-}

$_6$alkyloxy, C_{1-6}alkyloxycarbonylC_{1-6}alkylthio, aryl, Het^2, aryloxy, arylthio, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, Het^2C_{1-6}alkyloxy, Het^2C_{1-6}alkylthio, C_{1-6}alkyl-S(=O)$_2$-oxy, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, C_{1-6}alkyloxyC_{1-6}alkylcarbonylamino, mono- or di(aryl)amino, mono- or di(arylC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyloxyC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkylthioC_{1-4}alkyl)amino, mono- or di(Het^2C_{1-4}alkyl)amino, R^{11}-(C=O)-NH-, R^{12}-NH-(C=O)-NH-, R^{14}-S(=O)$_2$-NH-, C_{1-6}alkyl-P(O-R^{15})2=O, C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O or a radical of formula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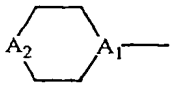
or


(c-2),

with A_1 being CH_2 or N, and A_2 being CH_2, NR^{13}, S or O, provided that when A_1 is CH_2 then A_2 is other than CH_2, said radical (c-1) and (c-2) being optionally substituted with one or two substituents each independently selected from H, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-4}alkyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyloxycarbonylC_{1-4}alkyl, aminoC_{1-6}alkyl, carbonyl, hydroxy, cyano, $CONR^{16}R^{17}$ with R^{16} and R^{17} being independently H or alkyl, mono or di(C_{1-4}alkyl)aminoalkyl, 4-hydroxy-4-phenyl or 4-cyano-4-phenyl;

or R^2 and R^3 may be taken together to form a bivalent radical of formula

$$-(CH_2)_t-CH_2-A_3-CH_2- \text{ (d-1)} \qquad \text{or} \qquad -CH=CH-CH=CH- \text{ (d-2)}$$

with t being an integer of 0, 1 or 2 and A_3 being CH_2, O, S, NR^{7a} or N[C(=O)R^{8a}] and wherein each hydrogen in said formula (d-1) or (d-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^4 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, amino, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl or aryl;

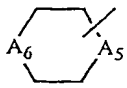
or R^4 and R^3 may be taken together to form a bivalent radical of formula

$-(CH_2)_t-CH_2-A_4-CH_2-$ (e-1) or CH=CH-CH=CH- (e-2)

with t being an integer of 0, 1 or 2 and A_4 being CH_2, O, S, NR^{7b} or $N[C(=O)R^{8b}]$ and wherein each hydrogen in said formula (e-1) or (e-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^5 and R^6 each independently are hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^{5a} and R^{6a} each independently are hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkylthio, amino, mono-or di(C_{1-4}alkyl)amino or a radical of formula



(f-1)

with A_5 and A_6 each independently being CH_2, NR^{13} or O;

R^7, R^{7a} and R^{7b} each independently are hydrogen, formyl or C_{1-4}alkyl;

R^8, R^{8a} and R^{8b} each independently are hydrogen or C_{1-4}alkyl;

R^9 is hydrogen, hydroxy, C_{1-4}alkyloxy, carboxylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy or arylC_{1-4}alkyloxy;

R^{10} is hydrogen, carboxyl or C_{1-4}alkyl;

R^{11} is hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkyl-$S(=O)_2$-, aryl or Het^3; C_{1-4}alkyloxy; C_{2-4}alkenyl; arylC_{2-4}alkenyl; Het^3C_{2-4}alkenyl; C_{2-4}alkynyl; Het^3C_{2-4}alkynyl, arylC_{2-4}alkynyl; C_{3-6}cycloalkyl; aryl; naphthyl or Het^3;

R^{12} is C_{1-4}alkyl, arylC_{1-4}alkyl, aryl, arylcarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkyloxycarbonylC_{1-4}alkyl;

R^{13} is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

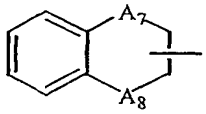
R^{14} is C_{1-4}alkyl optionally substituted with aryl or Het^4; polyhaloC_{1-4}alkyl or

C_{2-4}alkenyl optionally substituted with aryl or Het^4;

R^{15} is C_{1-4} alkyl;

Het^1 and Het^2 each independently are a heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl or 2-oxo-1,2-dihydro-quinolinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^3 is a monocyclic or bicyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl or a radical of formula



(g-1),

with A_7 or A_8 each independently being selected from CH_2 or O;
each of said monocyclic or bicyclic heterocycles may optionally be substituted with one, two or three substituents each independently selected from halo, hydroxy,C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^4 is a monocyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^5 is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl or oxazolyl;

aryl is phenyl optionally substituted with one, two or three substituents each independently selected from halo; hydroxy; carboxyl; cyano; formyl; nitro; amino; mono- or di(C_{1-4}alkyl)amino; C_{1-4}alkylcarbonylamino; mono- or di(C_{1-4}alkyl)aminocarbonylamino; C_{1-4}alkyl-S(=O)$_2$-NH-; C_{1-6}alkyloxy; C_{1-6}alkyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; phenyl or phenyloxy;

3. Compounds as claimed in claim 1 wherein

Q is halo, C_{1-6}alkyl or C_{2-6}alkenyl ;

X is (a-2) with q and r being 0 and Z being O, S or SO;

R_1 is aryl;

R_2 is selected from formyl; C_{1-6}alkyloxycarbonylalkyl; Het^2; Het^2C_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from hydroxy or halo;

R_3 is selected from formyl; C_{1-6}alkyl optionally substituted with one or two C_{1-6}alkyloxy;

R_4 is hydrogen.

4. Compounds as claimed in any one of claims 1 and 3 wherein Q is iodo.

5. Compounds as claimed in any one of claims 1 to 4 wherein Q is iodo, X-R_1 is a 3,5-dimethylphenylthio or a 3,5-dimethylphenyloxy and R_2 is a hydroxymethyl or a N-morpholinomethyl, or a 3-phenylproyl or a furan-2-yl-methylthiomethyl.

6. Compounds as claimed in any one of claims 1 to 5 wherein Q is iodo, X-R_1 is a 3-(2-cyano-vinyl)-5-iodophenyloxy or 5-bromo-3-(2-cyano-vinyl) and R_2 is ethyl.

7. Compounds as claimed in any one of claims 1 to 4 wherein the compounds are 242, 255, 43, 264, 124, 249, 298, 326, 133, 241, 253, 306, 328, 46, 105,234, 254, 256, 272, 284, 296, 319, 83, 88, 108, 109, 115, 277, 286, 299, 45, 85, 86, 231, 244, 297, 250, 257, 307, 324, 81, 92, 140, 143, 217, 221, 230, 232, 245, 309, 321, 322, 31, 218, 222, 314, 8, 99, 121, 219, 233, 280, 551, 470, 375, 483, 547, 606,618, 662, 694, 700, 709, 713 of table 1.

8. The use of a compound as claimed in anyone of claims 1 to 7 for the manufacture of a medicine for the treatment of subjects suffering from Human Immuno Deficiency Virus infection.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as defined in anyone of claims 1 to 8.

10. A process for preparing a pharmaceutical composition as defined in claim 7, characterized in that a therapeutically effective amount of a compound as defined in anyone of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.

11. The combination of a compound of formula (I) as defined in claim 1 and other antiretroviral compounds.

12. A product containing (a) a compound of formula (I) as defined in claim 1 and (b) another antiretroviral compound as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound of formula (I) as defined in claim 1 and (b) another antiretroviral compound.

5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(51) International Patent Classification[7]: C07D 401/12, 213/78, 407/06, 417/06, 401/06, 213/71, 405/04, 213/82, 213/70, 213/69, 409/12, 417/12, 405/12, 491/04, 215/22

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(71) Applicants *(for all designated States except US)*: **JANSSEN PHARMACEUTICA N.V.** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS)** [FR/FR]; 3, rue Michel Ange, F-75794 Paris Cédex 16 (FR). **INSTITUT CURIE** [FR/FR]; 26, rue d'Ulm, F-75005 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GUILLEMONT, Jérôme** [FR/FR]; 51 Bis Route de Muids, F-27430 (FR). **BENJAHAD, Abdellah** [FR/FR]; 84, rue de Verdun, F-94500 Champigny-Sur-Marne (FR). **MABIRE, Dominique** [FR/FR]; 14, rue Jean Moulin, F-27230 La Saussaye (FR). **N'GUYEN, Chi, Hung** [FR/FR]; 96, Avenue due Président Kennedy, F-92160 Antony (FR). **GRIERSON, David** [CA/FR]; 10, rue Camille Saint Saens, F-78530 Buc (FR). **MONNERET, Claude** [FR/FR]; 9, Avenue Lamoricière, F-75012 Paris (FR). **BISAGNI, Emile** [FR/FR]; 16, rue Bossuet, F-91400 Orsay (FR). **SANZ, Gérard** [FR/FR]; 6, rue Alfred Dunet, F-76240 Le Mesnil Esnard (FR). **DECRANE, Laurence** [FR/FR]; 13 Allée de la Trésorerie, F-27100 Le Vaudreuil (FR).

(74) Agents: **MARTIN, Jean-Jacques** et al.; Cabinet Regimbeau, 20, rue de Chazelles, F-75847 Paris Cedex 17 (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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— *of inventorship (Rule 4.17(iv)) for US only*

Published:
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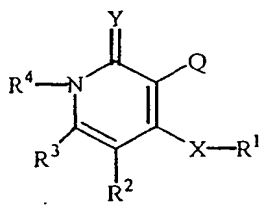
8 August 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/024650 A3

(54) Title: PYRIDINONE AND PYRIDINETHIONE DERIVATIVES HAVING HIV INHIBITING PROPERTIES



(1)

(57) Abstract: The present invention is concerned among others with compounds of formula (I), the N-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and stereochemically isomeric forms thereof, wherein Q is halo, C_{1-6} alkyl or C_{2-6} alkenyl; X is (a-2) with q and r being O and Z being O, S or SO; R_1 is aryl; R_2 is selected from formyl; C_{1-6}alkyloxycarbonylalkyl; Het[2]; Het[2]C_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from hydroxy, and halo; R_3 is selected from formyl; C_{1-6}alkyl optionally substituted with one or two C_{1-6}alkyloxy; R_4 is hydrogen, with HIV inhibiting properties.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02082

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D213/78 C07D407/06 C07D417/06 C07D401/06
C07D213/71 C07D405/04 C07D213/82 C07D213/70 C07D213/69
C07D409/12 C07D417/12 C07D405/12 C07D491/04 C07D215/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 05113 A (CENTRE NAT RECH SCIENT ;BISAGNI EMILE (FR); DOLLE VALERIE (FR); NG) 13 February 1997 (1997-02-13) cited in the application examples 15,16 tables 2,3,5 claims 1,23 ---	1,2,7-13
X	WO 99 55676 A (AUBERTIN ANNE MARIE ;BISAGNI EMILE (FR); DOLLE VALERIE (FR); GRIER) 4 November 1999 (1999-11-04) cited in the application examples 1,2 table 3 claims 1,9 --- -/--	1,8-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 February 2002	07. 06. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02082

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D407/04 C07D409/04 C07D213/89 C07D215/36 C07D407/14
C07D407/12 C07D413/06 C07D413/14 C07D213/85 C07D213/80
C07D413/12 C07D213/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 37977 A (HOECHST AG ;KIRSCH REINHARD (DE); KLEIM JOERG PETER (DE); RIESS GU) 16 October 1997 (1997-10-16) example 5; table 3 tables 1,2 claims 1,6 --- -/--	1,2,7-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later.than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 February 2002	07 06. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOLLE V ET AL: "A NEW SERIES OF PYRIDINONE DERIVATIVES AS POTENT NON-NUCLEOSIDE HUMAN IMMUNODEFICIENCY VIRUS TYPE U SPECIFIC REVERSE TRANSCRIPTASE INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 23, 15 October 1995 (1995-10-15), pages 4679-4686, XP002002675 ISSN: 0022-2623 example 17 table 1 ---	1,7-13
X	DATABASE CAOLD [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOLDER C.R. ET AL: "Tautomerism of Hydroxypyridines - (II) Bromination of 2,4-Dihydroxypyridines and its Ethyl Derivatives" retrieved from STN Database accession no. CA55:1608f XP002190994 CAS RN: 100960-13-2 ---	1,2
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X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STADLBAUER, WOLFGANG: "Synthesis of 4-azido-2(1H)-quinolones" retrieved from STN Database accession no. 107:134174 XP002190977 CAS RN: 110229-56-6 abstract & MONATSH. CHEM. (1986), 117(11), 1305-23, --- -/--	1,2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; EARL, RICHARD A. ET AL: "The preparation of 2(1H)-pyridinones and 2,3-dihydro-5(1H)- indolizinones via transition metal mediated cocyclization of alkynes and isocyanates. A novel construction of the antitumor agent camptothecin" retrieved from STN Database accession no. 102:6913 XP002190978 CAS RN: 88761-67-9; 88761-36-8; 92957-95-4 abstract & J. ORG. CHEM. (1984), 49(25), 4786-800, ---	1,2
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; EARL, RICHARD A. ET AL: "Cobalt-catalyzed cocyclizations of isocyanato alkynes: a regiocontrolled entry into 5-indolizinones. Application to the total synthesis of camptothecin" retrieved from STN Database accession no. 100:85968 XP002190979 CAS RN: 88761-37-9; 88761-41-5; 88761-36-8; 88761-40-4 abstract & J. AM. CHEM. SOC. (1983), 105(23), 6991-3, ---	1,2
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; FITTON, ALAN O. ET AL: "Reactions of formylchromone derivatives. Part 1. Cycloadditions to 2- and 3-(aryliminomethyl)chromones" retrieved from STN Database accession no. 88:22533 XP002190980 CAS RN: 65160-31-8; 6510-32-9 abstract & J. CHEM. SOC., PERKIN TRANS. 1 (1977), (12), 1450-2, --- -/--	1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/02082

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MOSHCHITSKII, S. D. ET AL: "Reactions of diethyl 2,3,5,6-tetrachloro-4-pyridylmalonate" retrieved from STN Database accession no. 73:120466 XP002190981 CAS RN: 29168-04-5; 29168-05-6 abstract & KHIM. GETEROTSIKL. SOEDIN. (1970), (6), 791-3, ---	1,2
A	WO 00 00475 A (DU PONT PHARM CO) 6 January 2000 (2000-01-06) page 16; example 12 table 2 claims 1,12 ---	1,8-13
A	MAO C ET AL: "Rational design of N-[2-(2,5-dimethoxyphenylethyl)]-N'-[2-(5-bromopyr idyl)]-thiourea (HI-236) as a potent non-nucleoside inhibitor of drug-resistant human immunodeficiency virus" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 9, no. 11, 7 June 1999 (1999-06-07), pages 1593-1598, XP004169626 ISSN: 0960-894X page 1594, table 1: HI-280; HI-281 abstract -----	1,8-13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 01/02082

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3(all partially); 4-6; 7-13 (all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3 (all partially); 4-6; 7-13 (all partially)

   Compounds according to formula (I) of claim 1 for which Q is halogen as well as their pharmaceutical use and compositions.

2. Claims: 1, 7-13 (all partially)

   Compounds according to formula (I) of claim 1 for which Q is hydrogen as well as their pharmaceutical use and compositions.

3. Claims: 1-3 (all partially); 7-13 (all partially)

   Compounds according to formula (I) of claim 1 for which Q is C1-6alkyl optionally substituted according to claim 1; C1-6alkyloxyC1-6alkyl; C1-6alkylthioC1-6alkyl; C1-6alkylcarbonyl; C1-6alkyloxycarbonyl; hydroxyC1-6alkyl; polyhaloC1-6alkyl; C1-6alkyloxycarbonylC1-6alkyl; C1-6alkyloxyC1-6alkyloxycarbonyl; C2-6alkenyl optionally substituted according to claim 1; C2-6alkinyl optionally substituted according to claim 1; C3-6cycloalkyl optionally substituted according to claim 1; cyano; carboxyl; formyl; R5R6N-C(=O); R5R6N-C(=O)-C1-6alkyl; aryl; arylC1-6alkyl; arylcarbonyl; arylC1-6alkyloxycarbonyl; Het1; Het1C1-6alkyl; Het1carbonyl; Het1C1-6alkyloxycarbonyl as well as their pharmaceutical use and compositions.

4. Claims: 1,2,8-13 (all partially)

   Compound according to formula (I) of claim 1 for which Q is di(C1-4alkyl)amino, N-hydroxy-imino, N-C1-C4alkyloxy-imino as well their pharmaceutical use and compositions.

5. Claims: 1,2,7-13 (all partially)

   Compounds according to formula (I) of claim 1 for which Q is C1-6alkyloxy, aryloxy, Het1oxy as well as their pharmaceutical use and compositions.

6. Claims: 1,2,7-13 (all partially)

   Compounds according to formula (I) of claim 1 for which Q is

C1-6alkylthio, C1-6alkyl-S(=O)-, C1-6alkyl-S(=O)2-, C1-6alkyloxycarbonylC1-6alkylthio, aminocarbonylC1-6alkylthio, arylthio, Het1thio as well as their pharmaceutical use and compositions.

7. Claims: 1,2,7-13 (all partially)

Compounds according to formula (I) of claim 1 for which Q is C1-6alkyl-P(OR15)2=O or C1-6alkyl-P(O-C1-6alkyl-O)=O as well as their pharmaceutical use and compositions.

8. Claims: 1,2,8-13 (all partially)

Compounds according to formula (I) of claim 1 for which Q and X-R1 are taken together with the pyridinone to form a tricyclic heterocycle of formula (h-1) as well as their pharmaceutical use and compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 01/02082

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9705113 A	13-02-1997	FR 2737496 A1	07-02-1997
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		EP 1091939 A1	18-04-2001
		WO 0000475 A1	06-01-2000
		US 6090821 A	18-07-2000

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(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
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(51) International Patent Classification[7]: C07D 401/12, 213/78, 407/06, 417/06, 401/06, 213/71, 405/04, 213/82, 213/70, 213/69, 409/12, 417/12, 405/12, 491/04, 215/22

(21) International Application Number: PCT/IB01/02082

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18 September 2001 (18.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
00402583.9 19 September 2000 (19.09.2000) EP

(71) Applicants *(for all designated States except US)*: **JANSSEN PHARMACEUTICA N.V.** [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE). **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS)** [FR/FR]; 3, rue Michel Ange, F-75794 Paris Cedex 16 (FR). **INSTITUT CURIE** [FR/FR]; 26, rue d'Ulm, F-75005 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GUILLEMONT, Jérôme** [FR/FR]; 51 Bis Route de Muids, F-27430 (FR). **BENJAHAD, Abdellah** [FR/FR]; 84, rue de Verdun, F-94500 Champigny-Sur-Marne (FR). **MABIRE, Dominique** [FR/FR]; 14, rue Jean Moulin, F-27230 La Saussaye (FR). **N'GUYEN, Chi, Hung** [FR/FR]; 96, Avenue due Président Kennedy, F-92160 Antony (FR). **GRIERSON, David** [CA/FR]; 10, rue Camille Saint Saens, F-78530 Buc (FR). **MONNERET, Claude** [FR/FR]; 9, Avenue Lamoricière, F-75012 Paris (FR). **BISAGNI, Emile** [FR/FR]; 16, rue Bossuet, F-91400 Orsay (FR). **SANZ, Gérard** [FR/FR]; 6, rue Alfred Dunet, F-76240 Le Mesnil Esnard (FR). **DECRANE, Laurence** [FR/FR]; 13 Allée de la Trésorerie, F-27100 Le Vaudreuil (FR).

(74) Agents: **MARTIN, Jean-Jacques** et al.; Cabinet Regimbeau, 20, rue de Chazelles, F-75847 Paris Cedex 17 (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
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— *with amended claims*

(88) Date of publication of the international search report:
8 August 2002

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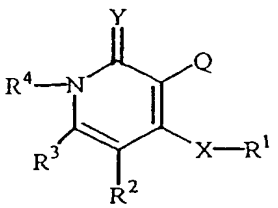
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/024650 A3

(54) Title: PYRIDINONE AND PYRIDINETHIONE DERIVATIVES HAVING HIV INHIBITING PROPERTIES

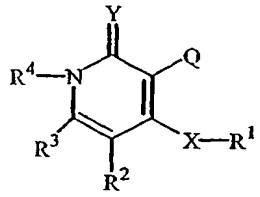


(I)

(57) Abstract: The present invention is concerned among others with compounds of formula (I), the N-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and stereochemically isomeric forms thereof, wherein Q is halo, C_{1-6} alkyl or C_{2-6} alkenyl; X is (a-2) with q and r being 0 and Z being O, S or SO; R_1 is aryl; R_2 is selected from formyl; C_{1-6}alkyloxycarbonylalkyl; Het^2; Het^2C_{1-6}alkyl, C_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from hydroxy, and halo; R_3 is selected from formyl; C_{1-6}alkyl optionally substituted with one or two C_{1-6}alkyloxy; R_4 is hydrogen, with HIV inhibiting properties.

AMENDED CLAIMS
[received by the International Bureau on 11 July 2002 (11.07.02);
original claims 1, 2, 9 and 10 amended; remaining claims unchanged (14 pages)]

1. Compounds of formula (I)



(I),

the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and stereochemically isomeric forms thereof, wherein

Y is O or S;

Q is halo; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkylthioC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl-S(=O)-; C_{1-6}alkyl-S(=O)$_2$-; hydroxyC_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkylthio; aminocarbonyl$_6$$C_{1-6}$alkylthio; C_{1-6}alkyloxyC_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, -COOH, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{3-6}cycloalkyl optionally substituted with C_{1-4}alkyl; cyano; carboxyl; formyl; R^5R^6N-C(=O)-; R^5R^6N-C(=O)-C_{1-6}alkyl; *N*-hydroxy-imino; *N*-C_{1-4}alkyloxy-imino; aryloxy; arylthio; arylC_{1-6}alkyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with hydroxy and aryl; Het^1; Het^{1}oxy; Het^{1}thio; Het^1C_{1-6}alkyl; Het^{1}carbonyl; Het^1C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-P(OR^{15})$_2$=O or C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O;

X is a bivalent radical of formula

-$(CH_2)_p$- (a-1) or

-$(CH_2)_q$-Z-$(CH_2)_r$- (a-2);

wherein p is an integer of value 1 to 5;

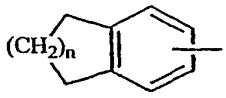
q is an integer of value 0 to 5;

r is an integer of value 0 to 5;

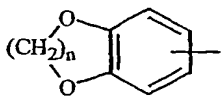
Z is O, S, NR^7, C(=O), S(=O), S(=O)$_2$, $CHOR^{13}$, CH=CH, $CH(NR^7R^8)$ or CF_2;

and wherein each hydrogen atom may be replaced by C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

R^1 is C_{3-6}cycloalkyl, C_{1-6}alkenyl, aryl or a monocyclic or bicyclic heterocycle selected from pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, or a radical of formula


(b-1)

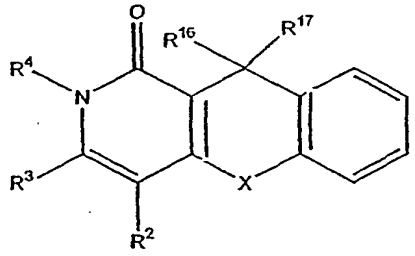
or


(b-2)

with n being an integer of 1 or 2,

said monocyclic or bicyclic heterocycle or said radical of formula (b-1) or (b-2) optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, polyhaloC_{1-4}alkyl or phenyl;

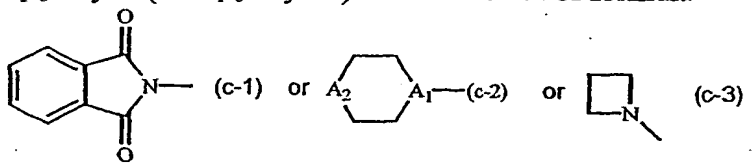
or Q and X-R^1 may be taken together with the pyridinone to form a tricyclic heterocycle of formula


(h-1)

with R^{16} and R^{17} being C_{1-6}alkyl or forming together =O.

R^2 and R^3 each independently are selected from hydrogen; halo; formyl; cyano; azido; hydroxy; oxiranyl; amino; mono- or di(C_{1-4}alkyl)amino; formylamino; mercapto(C_{1-6})alkyl; hydrazino; $R^{5a}R^{6a}$N-C(=O)-; R^9-N=C(R^{10})-; C_{2-6}alkenyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, di(C_{1-4}alkyl)carbamoyl, [di(C_{1-4}alkyl)amino(C_{1-6}alkyl)](C_{1-4}alkyl)carbamoyl, [di(C_{1-4}alkyl)amino(C_{1-6}alkyl)](arylC_{1-4}alkyl)carbamoyl, di(C_{1-4}alkyloxy)(C_{1-4}alkyl)carbamoyl, (cyanoC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl, *N*-hydroxy-imino, aryl, Het^2, Het^2carboxamido, Het^2(C_{1-6}alkyl)carbamoyl; C_{2-6}alkynyl optionally substituted with one or two substituents each independently selected

from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{1-6}alkyloxy; hydroxyC_{1-6}alkyloxy; aminoC_{1-6}alkyloxy; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; arylcarbonyl; Het^2carbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxy; aryl; aryloxy; arylC_{1-6}alkyloxy; arylthio; arylC_{1-6}alkylthio; mono- or di(aryl)amino; Het^2; Het^2oxy; Het^2thio; Het^2C_{1-6}alkyloxy; Het^2C_{1-6}alkylthio; Het^2SO_2; Het^2SO; mono- or di(Het^2)amino; C_{3-6}cycloalkyl; C_{3-6}cycloalkyloxy; C_{3-6}cycloalkylthio; C_{1-6}alkylthio; hydroxyC_{1-6}alkylthio; aminoC_{1-6}alkylthio; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, carboxyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulfonyl, C_{1-6}alkycarbamoylC_{1-4}alkylthio, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkylthio C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, aminocarbonyloxy, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonylC_{1-6}alkylthio, aryl, Het^2, aryloxy, arylthio, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, Het^2C_{1-6}alkyloxy, Het^2C_{1-6}alkylthio, C_{1-6}alkyl-S(=O)$_2$-oxy, amino, mono- or di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkylthio, [di(C_{1-6}alkyl)amino(C_{1-6}alkyl)](C_{1-6}alkyl)amino, di(cyanoC_{1-6}alkyl)amino, C_{1-6}alkyloxycarbonylamino, C_{1-6}alkyloxyC_{1-6}alkylcarbonylamino, mono- or di(aryl)amino, mono- or di(arylC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyloxyC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkylthioC_{1-4}alkyl)amino, mono- or di(Het^2C_{1-4}alkyl)amino, (Het^2C_{1-4}alkyl)(C_{1-4}alkyl)amino, (cyanoC_{1-6}alkyl)(C_{1-6}alkyl)amino, C_{3-6}cycloalkylthio, R^{11}-(C=O)-NH-, R^{12}-NH-(C=O)-NH-, R^{14}-S(=O)$_2$-NH-, C_{1-6}alkyl-P(O-R^{15})2=O, C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O or a radical of formula



with A_1 being CH or N, and A_2 being CH_2, NR^{13}, S or O, provided that when A_1 is CH then A_2 is other than CH_2, said radical (c-1), (c-2) and (c-3) being optionally substituted with one or two substituents each independently selected from H, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6} alkyloxycarbonylC_{1-4}alkyl, aminoC_{1-6}alkyl, C_{1-4}alkylcarbonyl, arylcarbonyl, aryl, Het^1, Het^1-(C=O)-, hydroxy, cyano, C_{1-4}alkylcyano, $CONR^{16}R^{17}$ with R^{16}

and R^{17} being independently H or alkyl, mono or di(C_{1-4}alkyl)aminoalkyl, 4-hydroxy-4-phenyl or 4-cyano-4-phenyl;

or R^2 and R^3 may be taken together to form a bivalent radical of formula

$-(CH_2)_t-CH_2-A_3-CH_2-$ (d-1) or $-CH=CH-CH=CH-$ (d-2)

with t being an integer of 0, 1 or 2 and A_3 being CH_2, O, S, NR^{7a} or $N[C(=O)R^{8a}]$ and wherein each hydrogen in said formula (d-1) or (d-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^4 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, amino, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl or aryl;

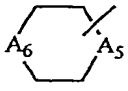
or R^4 and R^3 may be taken together to form a bivalent radical of formula

$-(CH_2)_t-CH_2-A_4-CH_2-$ (e-1) or $-CH=CH-CH=CH-$ (e-2)

with t being an integer of 0, 1 or 2 and A_4 being CH_2, O, S, NR^{7b} or $N[C(=O)R^{8b}]$ and wherein each hydrogen in said formula (e-1) or (e-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^5 and R^6 each independently are hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^{5a} and R^{6a} each independently are hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkylthio, amino, mono-or di(C_{1-4}alkyl)amino or a radical of formula



(f-1)

with A_5 and A_6 each independently being CH_2, NR^{13} or O;

R^7, R^{7a} and R^{7b} each independently are hydrogen, formyl or C_{1-4}alkyl;

R^8, R^{8a} and R^{8b} each independently are hydrogen or C_{1-4}alkyl;

R^9 is hydrogen, hydroxy, C_{1-4}alkyloxy, carboxylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy or arylC_{1-4}alkyloxy;

R^{10} is hydrogen, carboxyl or C_{1-4}alkyl;

R^{11} is hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkyl-$S(=O)_2$-, aryl or Het^3; C_{1-4}alkyloxy; C_{2-4}alkenyl; arylC_{2-4}alkenyl; Het^3C_{2-4}alkenyl; C_{2-4}alkynyl; Het^3C_{2-4}alkynyl, arylC_{2-4}alkynyl; C_{3-6}cycloalkyl; aryl; naphthyl or Het^3;

R^{12} is C_{1-4}alkyl, arylC_{1-4}alkyl, aryl, arylcarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkyloxycarbonylC_{1-4}alkyl;

R^{13} is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

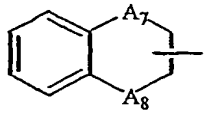
R^{14} is C_{1-4}alkyl optionally substituted with aryl or Het^4; polyhaloC_{1-4}alkyl or C_{2-4}alkenyl optionally substituted with aryl or Het^4;

R^{15} is C_{1-4} alkyl;

Het^1 and Het^2 each independently are a heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyrimidinyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl, morpholinyl, thiomorpholinyl triazolyl, tetrazolyl, pyrrolyl, pyrazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, indolyl, indazolyl, benzodioxanyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, imidazopyridinyl, dihydropyrrolyl or dihydroisoxazolyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from O, S, halo, formyl, amino, hydroxy, cyano, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, carboxyC_{1-4}alkyl, carbamoylC_{1-4}alkyl, carbamoylC_{1-4}alkoxy, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxyC_{1-4}alkyl, cyanoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, $-OCONH_2$, C_{1-4}alkoxyC_{1-4}alkyl,

aryl, Het^2C_{1-4}alkyl , polyhaloC_{1-4}alkyl, C_{3-6}cycloalkyl or arylC_{2-6}alkenyl;

Het^3 is a monocyclic or bicyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl or a radical of formula



(g-1),

with A_7 or A_8 each independently being selected from CH_2 or O;

each of said monocyclic or bicyclic heterocycles may optionally be substituted with one, two or three substituents each independently selected from halo, hydroxy,C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^4 is a monocyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^5 is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, tetrazolyl, piperidinyl, morpholinyl or pyrrolidinyl;

aryl is phenyl optionally substituted with one, two or three substituents each independently selected from halo; hydroxy; carboxyl; cyano; formyl; acetyl; nitro; amino; mono- or di(C_{1-4}alkyl)amino; C_{1-4}alkylcarbonylamino; mono- or di(C_{1-4}alkyl)aminocarbonylamino; C_{1-4}alkyl-S(=O)$_2$-NH-; Het^5(=S)-S-C_{1-4}alkyl ; C_{1-6}alkyloxy; sulfamoyl; (C_{1-4}alkyl)sulfamoyl; arylsulfamoyl; Het^2sulfamoyl; O-P=OR^{15}; C_{1-6}alkyl optionally substituted with halo, hydroxy, cyano, nitro, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{2-6}alkenyloxy, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonylthio, *N*-hydroxyimino, phenyl or Het^5; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, nitro, formyl, amino, mono-

or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; phenyl; phenyloxy; phenyl(C_{1-4}alkyl)thioC_{1-4}alkyl; (C_{3-6})cyclohexylthioC_{1-4}alkyl or isoxazolinyl optionally substituted by C_{1-4}alkyloxycarbonyl or morpholinylC_{1-4}alkyl

provided that

5,6,7,8-tetrahydro-3-iodo-4-phenoxy-1-phenyl-2(1*H*)quinolinone;
3-iodo-6-methyl-4-phenoxy-2(1*H*)-pyridinone;
2-[(3,5,6-trifluoro-1,2-dihydro-2-oxo-4-pyridinyl)amino]benzoic acid;
1,2-dihydro-6-hydroxy-2-oxo-4-(2-phenylethyl)-3-pyridinecarbonitrile;
1,2-dihydro-6-hydroxy-2-oxo-4-(4-pyridinylmethyl)-3-pyridinecarbonitrile;
4-[(4-bromophenyl)methoxy]-3,5-diodo-1-methyl-2(1*H*)-pyridinone;
4-[(4-bromophenyl)methoxy]-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxylic acid; 1,2-dihydro-6-methyl-2-oxo-4-(phenylthio)-3-pyridinecarboxylic acid and the alkyl-4-arylthio-1,2-dihydro-5-methyl-6-methyl-2-oxo-3-pyridine carboxylate
3-bromo-4-[[[2-(3,4-dimethoxyphenyl)ethyl]amino]methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-1-methyl-4-phenoxy-2(1*H*)quinolinone;
1-ethyl-3-iodo-7-methoxy-4-phenoxy-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-(4-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
1-ethyl-3-iodo-7-methoxy-4-(4-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-(3-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
1-ethyl-3-iodo-7-methoxy-4-(3-methoxyphenoxy)-1-methyl-2(1*H*)quinolinone;
3-iodo-7-methoxy-4-phenoxy-2(1*H*)quinolinone;
4-(3-chloro-4-methoxyphenoxy)-3-iodo-7-methoxy-2(1*H*)quinolinone;
3-iodo-4-phenoxy-2(1*H*)quinolinone;
3-iodo-4-phenoxy-1-phenyl-2(1*H*)quinolinone;
3-iodo-4-4-phenoxy-1-méthyl-2(1*H*)quinolinone
3-iodo-4-(4-methylphenoxy)-2(1*H*)quinolinone;
3-iodo-4-(4-methoxyphenoxy)-2(1*H*)quinolinone;
are not included and
provided X is other than $-CH_2-NH-CH_2-CH_2-$ or $-NH-CH_2-$.

2. Compounds as claimed in claim 1 wherein

Q is halo; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkylthioC_{1-6}alkyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-S(=O)-; C_{1-6}alkyl-S(=O)$_2$-; hydroxyC_{1-6}alkyl; polyhaloC_{1-6}alkyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl; C_{1-6}alkyloxyC_{1-6}alkyloxycarbonyl; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino or aryl; C_{3-6}cycloalkyl optionally substituted with C_{1-4}alkyl; cyano; carboxyl; formyl; R^5R^6N-C(=O)-; R^5R^6N-C(=O)-C_{1-6}alkyl; *N*-hydroxy-imino; *N*-C_{1-4}alkyloxy-imino; aryloxy; arylthio; arylC_{1-6}alkyl; arylcarbonyl; arylC_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryl; Het^1; Het^1oxy; Het^1thio; Het^1C_{1-6}alkyl; Het^1carbonyl; Het^1C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl-P(OR^{15})$_2$=O or C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O;

X is a bivalent radical of formula

-$(CH_2)_p$- (a-1) or

-$(CH_2)_q$-Z-$(CH_2)_r$- (a-2);

wherein p is an integer of value 1 to 5;

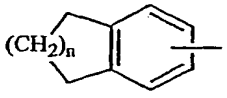
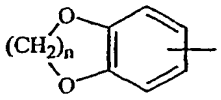
q is an integer of value 0 to 5;

r is an integer of value 0 to 5;

Z is O, S, NR^7, C(=O), S(=O), S(=O)$_2$, $CHOR^{13}$, CH=CH, $CH(NR^7R^8)$ or CF_2;

and wherein each hydrogen atom may be replaced by C_{1-4}alkyl or hydroxyC_{1-4}alkyl;

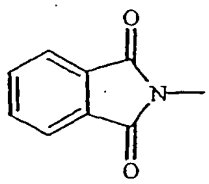
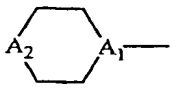
R^1 is C_{3-6}cycloalkyl, aryl or a monocyclic or bicyclic heterocycle selected from pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl, oxazolyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, or a radical of formula

 (b-1) or  (b-2)

with n being an integer of 1 or 2,

said monocyclic or bicyclic heterocycle or said radical of formula (b-1) or (b-2) optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, polyhaloC_{1-4}alkyl or phenyl;

R^2 and R^3 each independently are selected from hydrogen; halo; formyl; cyano; azido; hydroxy; oxiranyl; amino; mono- or di(C_{1-4}alkyl)amino; formylamino; $R^{5a}R^{6a}$N-C(=O)-; R^9-N=C(R^{10})-; C_{2-6}alkenyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{2-6}alkynyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, formyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, aryl or Het^2; C_{1-6}alkyloxy; hydroxyC_{1-6}alkyloxy; aminoC_{1-6}alkyloxy; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; arylcarbonyl; Het^2carbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylcarbonyloxy; aryl; aryloxy; arylC_{1-6}alkyloxy; arylthio; arylC_{1-6}alkylthio; mono- or di(aryl)amino; Het^2; Het^2oxy; Het^2thio; Het^2C_{1-6}alkyloxy; Het^2C_{1-6}alkylthio; mono- or di(Het^2)amino; C_{3-6}cycloalkyl; C_{3-6}cycloalkyloxy; C_{3-6}cycloalkylthio; C_{1-6}alkylthio; hydroxyC_{1-6}alkylthio; aminoC_{1-6}alkylthio; mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from halo, hydroxy, cyano, C_{1-6}alkyloxy, C_{1-6}alkylthio, hydroxyC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, aminocarbonyloxy, mono- or di(C_{1-4}alkyl)aminocarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyloxy, C_{1-6}alkyloxycarbonylC_{1-6}alkylthio, aryl, Het^2, aryloxy, arylthio, arylC_{1-6}alkyloxy, arylC_{1-6}alkylthio, Het^2C_{1-6}alkyloxy, Het^2C_{1-6}alkylthio, C_{1-6}alkyl-S(=O)$_2$-oxy, amino, mono- or di(C_{1-6}alkyl)amino, C_{1-6}alkyloxy-carbonylamino, C_{1-6}alkyloxyC_{1-6}alkylcarbonylamino, mono- or di(aryl)amino, mono- or di(arylC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyloxyC_{1-4}alkyl)amino, mono- or di(C_{1-4}alkylthioC_{1-4}alkyl)amino, mono- or di(Het^2C_{1-4}alkyl)amino, R^{11}-(C=O)-NH-, R^{12}-NH-(C=O)-NH-, R^{14}-S(=O)$_2$-NH-, C_{1-6}alkyl-P(O-R^{15})2=O, C_{1-6}alkyl-P(O-C_{1-6}alkyl-O)=O or a radical of formula


(c-1) or

(c-2),

with A_1 being CH_2 or N, and A_2 being CH_2, NR^{13}, S or O, provided that when A_1 is CH_2 then A_2 is other than CH_2, said radical (c-1) and (c-2) being optionally substituted with one or two substituents each independently selected from H, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-4}alkyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyloxycarbonylC_{1-4}alkyl, aminoC_{1-6}alkyl, carbonyl, hydroxy, cyano, $CONR^{16}R^{17}$ with R^{16} and R^{17} being independently H or alkyl, mono or di(C_{1-4}alkyl)aminoalkyl, 4-hydroxy-4-phenyl or 4-cyano-4-phenyl;

or R^2 and R^3 may be taken together to form a bivalent radical of formula

$$-(CH_2)_t-CH_2-A_3-CH_2- \text{ (d-1)} \qquad \text{or} \qquad -CH=CH-CH=CH- \text{ (d-2)}$$

with t being an integer of 0, 1 or 2 and A_3 being CH_2, O, S, NR^{7a} or $N[C(=O)R^{8a}]$ and wherein each hydrogen in said formula (d-1) or (d-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^4 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxycarbonylC_{1-6}alkyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, amino, mono- or di(C_{1-4}alkyl)amino, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl or aryl;

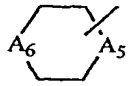
or R^4 and R^3 may be taken together to form a bivalent radical of formula

$$-(CH_2)_t-CH_2-A_4-CH_2- \text{ (e-1)} \qquad \text{or} \qquad CH=CH-CH=CH- \text{ (e-2)}$$

with t being an integer of 0, 1 or 2 and A_4 being CH_2, O, S, NR^{7b} or $N[C(=O)R^{8b}]$ and wherein each hydrogen in said formula (e-1) or (e-2) may be substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl, haloC_{1-4}alkylcarbonyl or arylcarbonyl;

R^5 and R^6 each independently are hydrogen, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^{5a} and R^{6a} each independently are hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkylthio, amino, mono-or di(C_{1-4}alkyl)amino or a radical of formula



(f-1)

with A_5 and A_6 each independently being CH_2, NR^{13} or O;

R^7, R^{7a} and R^{7b} each independently are hydrogen, formyl or C_{1-4}alkyl;

R^8, R^{8a} and R^{8b} each independently are hydrogen or C_{1-4}alkyl;

R^9 is hydrogen, hydroxy, C_{1-4}alkyloxy, carboxylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, C_{2-4}alkenyloxy, C_{2-4}alkynyloxy or arylC_{1-4}alkyloxy;

R^{10} is hydrogen, carboxyl or C_{1-4}alkyl;

R^{11} is hydrogen; C_{1-4}alkyl optionally substituted with cyano, C_{1-4}alkyloxy, C_{1-4}alkyl-$S(=O)_2$-, aryl or Het^3; C_{1-4}alkyloxy; C_{2-4}alkenyl; arylC_{2-4}alkenyl; Het^3C_{2-4}alkenyl; C_{2-4}alkynyl; Het^3C_{2-4}alkynyl, arylC_{2-4}alkynyl; C_{3-6}cycloalkyl; aryl; naphthyl or Het^3;

R^{12} is C_{1-4}alkyl, arylC_{1-4}alkyl, aryl, arylcarbonyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl or C_{1-4}alkyloxycarbonylC_{1-4}alkyl;

R^{13} is hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl;

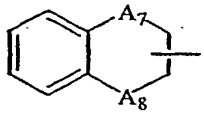
R^{14} is C_{1-4}alkyl optionally substituted with aryl or Het^4; polyhaloC_{1-4}alkyl or C_{2-4}alkenyl optionally substituted with aryl or Het^4;

R^{15} is C_{1-4} alkyl;

Het^1 and Het^2 each independently are a heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl,

benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl or 2-oxo-1,2-dihydro-quinolinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^3 is a monocyclic or bicyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, benzopyrrolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, quinolinyl, 2-oxo-1,2-dihydro-quinolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, imidazolidinyl, oxazolidinyl, thiazolidinyl, piperidinyl, hexahydropyrimidinyl, piperazinyl, hexahydropyridazinyl or a radical of formula



(g-1),

with A_7 or A_8 each independently being selected from CH_2 or O;
each of said monocyclic or bicyclic heterocycles may optionally be substituted with one, two or three substituents each independently selected from halo, hydroxy,C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^4 is a monocyclic heterocycle selected from pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, thiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, said heterocycle optionally being substituted with one, two or three substituents each independently selected from halo, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, C_{1-4}alkylcarbonyl or polyhaloC_{1-4}alkyl;

Het^5 is pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, pyrrolyl, thienyl, furanyl, imidazolyl, thiazolyl or oxazolyl;

aryl is phenyl optionally substituted with one, two or three substituents each independently selected from halo; hydroxy; carboxyl; cyano; formyl; nitro; amino; mono- or di(C_{1-4}alkyl)amino; C_{1-4}alkylcarbonylamino; mono- or di(C_{1-4}alkyl)aminocarbonylamino; C_{1-4}alkyl-S(=O)$_2$-NH-; C_{1-6}alkyloxy; C_{1-6}alkyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyloxy, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or

Het^5; C_{2-6}alkenyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; C_{2-6}alkynyl optionally substituted with halo, hydroxy, cyano, formyl, amino, mono- or di(C_{1-4}alkyl)amino, C_{1-6}alkyloxycarbonyl, C_{1-6}alkyloxy, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, *N*-hydroxy-imino, phenyl or Het^5; phenyl or phenyloxy;

3. Compounds as claimed in claim 1 wherein

Q is halo, C_{1-6}alkyl or C_{2-6}alkenyl ;

X is (a-2) with q and r being 0 and Z being O, S or SO;

R_1 is aryl;

R_2 is selected from formyl; C_{1-6}alkyloxycarbonylalkyl; Het^2; Het^2C_{1-6}alkyl; C_{1-6}alkylthio; C_{1-6}alkyl optionally substituted with one or two substituents each independently selected from hydroxy or halo;

R_3 is selected from formyl; C_{1-6}alkyl optionally substituted with one or two C_{1-6}alkyloxy;

R_4 is hydrogen.

4. Compounds as claimed in any one of claims 1 and 3 wherein Q is iodo.

5. Compounds as claimed in any one of claims 1 to 4 wherein Q is iodo, X-R_1 is a 3,5-dimethylphenylthio or a 3,5-dimethylphenyloxy and R_2 is a hydroxymethyl or a N-morpholinomethyl, or a 3-phenylproyl or a furan-2-yl-methylthiomethyl.

6. Compounds as claimed in any one of claims 1 to 5 wherein Q is iodo, X-R_1 is a 3-(2-cyano-vinyl)-5-iodophenyloxy or 5-bromo-3-(2-cyano-vinyl) and R_2 is ethyl.

7. Compounds as claimed in any one of claims 1 to 4 wherein the compounds are 242, 255, 43, 264, 124, 249, 298, 326, 133, 241, 253, 306, 328, 46, 105,234, 254, 256, 272, 284, 296, 319, 83, 88, 108, 109, 115, 277, 286, 299, 45, 85, 86, 231, 244, 297, 250, 257, 307, 324, 81, 92, 140, 143, 217, 221, 230, 232, 245, 309, 321, 322, 31,

218, 222, 314, 8, 99, 121, 219, 233, 280, 551, 470, 375, 483, 547, 606,618, 662, 694, 700, 709, 713 of table 1.

8. The use of a compound as claimed in anyone of claims 1 to 7 for the manufacture of a medicine for the treatment of subjects suffering from Human Immuno Deficiency Virus infection.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound as defined in anyone of claims 1 to 7.

10. A process for preparing a pharmaceutical composition as defined in claim 9, characterized in that a therapeutically effective amount of a compound as defined in anyone of claims 1 to 5 is intimately mixed with a pharmaceutically acceptable carrier.

11. The combination of a compound of formula (I) as defined in claim 1 and other antiretroviral compounds.

12. A product containing (a) a compound of formula (I) as defined in claim 1 and (b) another antiretroviral compound as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment.

13. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound of formula (I) as defined in claim 1 and (b) another antiretroviral compound.